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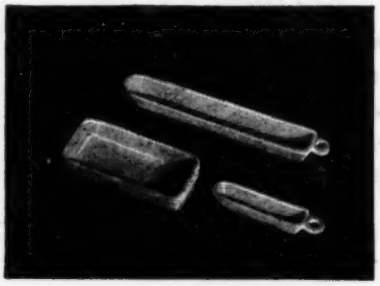

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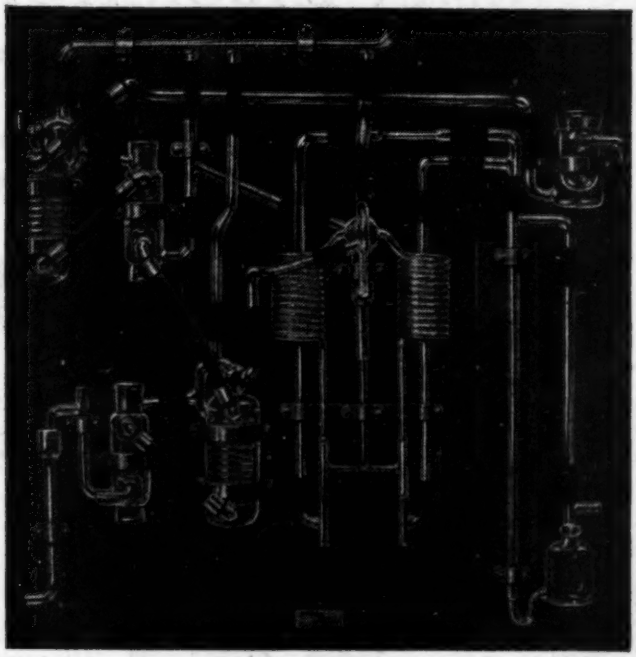

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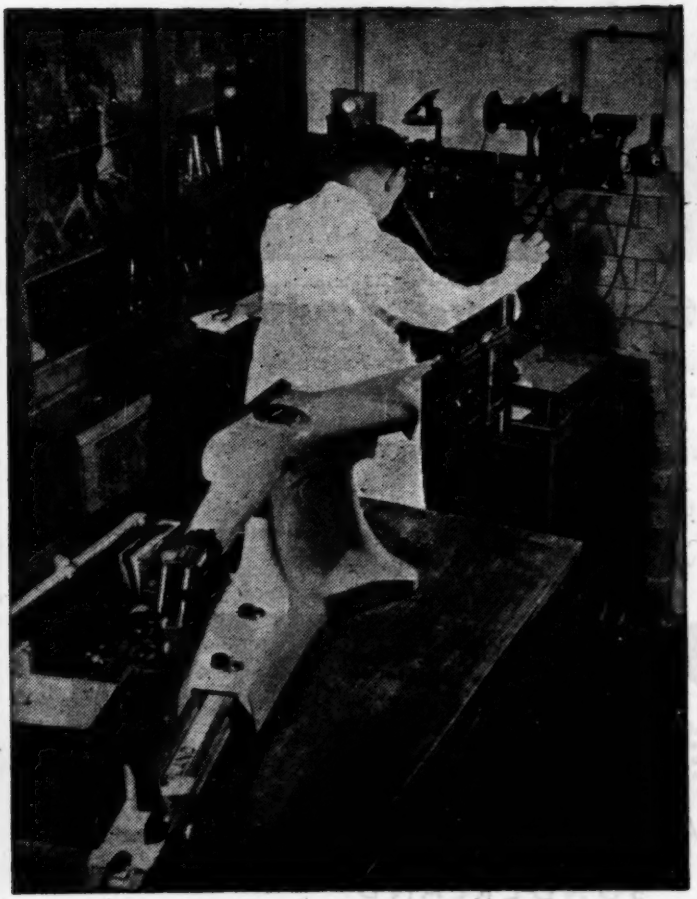

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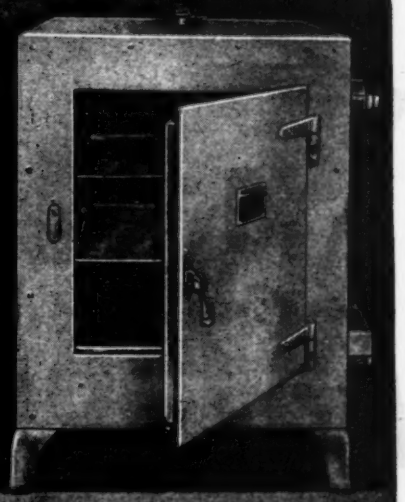

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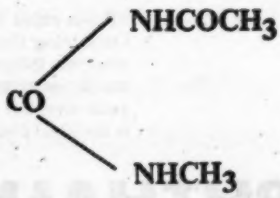

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Jones, K. M. See Hinkel, L. E.
Jones, W. E. See Booth, E.
Jones, W. G. M. See Haworth, W. N.
Kenner, G. W., Lythgoe, B., and Todd, A. R., 652.
Kenner, G. W. See also Baddiley, J.
Lythgoe, B. See Baddiley, J., and Kenner, G. W.
Magrath, D. See Albert, A.
Mann, F. G., and Haworth, R. C., 670.
Reed, R. A., 679.
Robinson, F. A. See Elliot, D. F.
Smith, F., 633.
Smith, F. See also Heslop, (Miss) D.
Stephenson, (Miss) E. F. M., 678.
Todd, A. R. See Baddiley, J., and Kenner, G. W.
Topham, A. See Baddiley, J.
Watkins, T. I. See Hinkel, L. E.
West, T. F., 642.

Finally, to settle the structure of our product (XVII; R = CN), we returned to the route from 4 : 4′-dibromodeoxybenzoin with two main aims, *viz.*, the isolation of specimens of *cis*- and *trans*-4 : 4′-dibromo-αβ-dimethylstilbene identical with those obtained from βγ-diphenyl-*n*-butane, and the isolation of a dibromodiethylstilbene, identical with that of Vargha and Kovács (*loc. cit.*), which could be converted into the same dicyanodiethylstilbene as that obtained from *p*-cyanopropiophenonehydrazone.

$$\underset{\text{(XVIII.)}}{C_6H_4Br\cdot CO\cdot CH_2\cdot C_6H_4Br} \longrightarrow \underset{\text{(XIX.)}}{C_6H_4Br\cdot CO\cdot CHR\cdot C_6H_4Br} \longrightarrow \underset{\text{(XX.)}}{C_6H_4Br\cdot CR'(OH)\cdot CHR\cdot C_6H_4Br} \longrightarrow C_6H_4Br\cdot CR'{:}CR\cdot C_6H_4Br \quad \text{(XXI.)}$$

An improved method for preparing 4 : 4′-dibromodeoxybenzoin, hitherto made by condensation of *p*-bromophenylacetyl chloride with bromobenzene, was found in the addition of the elements of water to 4 : 4′-*dibromotolan* which was readily available from 4 : 4′ : α : β-tetrabromo-αβ-diphenylethane.

4 : 4′-Dibromodeoxybenzoin (XVIII) reacted normally with methyl- and with ethyl-magnesium halides to form 1 : 2-*di*-(p-*bromophenyl*)-n-*propan*-2-*ol* (XX; R = H, R′ = Me) and the corresponding n-*butan*-2-*ol* (XX; R = H, R′ = Et), respectively; these were converted by anhydrous potassium hydrogen sulphate into the corresponding 4 : 4′-*dibromo*-α-*methyl*- and -α-*ethyl*-*stilbenes* (XXI; R = H) and these, in turn, were converted by way of the *nitriles* into 4 : 4′-*diamidino*-α-*methyl*- and -α-*ethyl*-*stilbenes*. *cis*- and *trans*-Forms were obtained in both series but could usually be separated by fractional crystallisation.

4 : 4′-*Dibromo*-α-*methyl*- and -α-*ethyl*-*deoxybenzoin* (XIX; R = Me or Et) were obtained from 4 : 4′-dibromodeoxybenzoin by means of methyl and ethyl iodide, respectively, and 4 : 4′-*dibromo*-α-*benzyldeoxybenzoin* by means of benzyl chloride. The first two compounds reacted normally with methyl- and ethyl-magnesium bromide, respectively. Some difficulty was experienced in dehydrating smoothly the resulting 2 : 3-*di*-(p-*bromophenyl*)-n-*butan*-2-*ol* and 3 : 4-*di*-(p-*bromophenyl*)-n-*hexan*-3-*ol*, (XX; R = R′ = Me) and (XX; R = R′ = Et). Phosphorus tribromide was useless, but acetic anhydride–acetyl chloride or anhydrous potassium hydrogen sulphate was better, and from the resulting oils 4 : 4′-dibromo-αβ-dimethyl- and -αβ-diethyl-stilbenes (XXI; R = R′ = Me or Et) were finally isolated in crystalline form. Treatment of the diethyl compound with bromine gave 4 : 4′ : γ : δ-*tetrabromo*-γδ-*diphenyl*-n-*hexane*.

In this series of experiments, the possibility of the type of rearrangement recorded by Földi (*Ber.*, 1941, 74, 930), *e.g.*

$$CH_3\cdot O\cdot C_6H_4\cdot CHCl\cdot CO\cdot C_6H_4\cdot O\cdot CH_3 \xrightarrow{2\,C_2H_5MgX} CH(C_6H_4\cdot O\cdot CH_3)_2\cdot CEt_2\cdot OH$$

was not overlooked but unsymmetrically substituted ethylenes were not found in the dehydration products.

Experimental.

Bromination of γδ-*Diphenyl*-n-*hexane*.—*Solid hydrocarbon.* (*a*) The hydrocarbon (2·3 g.), acetic acid (21 c.c.), and bromine (9·0 g.) were heated under reflux for 4 hours. After cooling, a white crystalline solid (2·8 g.), m. p. 150—190°, separated. Division into two components by washing with ether, followed by separate fractional crystallisation from acetic acid, gave the *dibromo*- (0·4 g.), m. p. 170—172° (Found: Br, 40·2. $C_{18}H_{20}Br_2$ requires Br, 40·4%), and the *hexabromo*-compound, m. p. 215° (decomp.) (Found: Br, 67·1. $C_{18}H_{16}Br_6$ requires Br, 67·2%).

(*b*) The hydrocarbon (10 g.), bromine (33·6 g.), and chloroform (50 c.c.) were heated under reflux for 4 hours, and the solvent then removed by distillation. The solid which separated recrystallised from glacial acetic acid to give the above dibromo-compound (10·2 g., 64·5%).

Liquid hydrocarbon. The hydrocarbon (10 g.), bromine (33·6 g.), and acetic acid (87 c.c.) were heated under reflux until the colour of the bromine had disappeared. When the hot liquors were seeded with a specimen of the hexabromo-compound, this separated in a pure form (4·1 g.), m. p. 215° (decomp.).

4 : 4′-*Dicyano*-γδ-*diphenyl*-n-*hexane*.—Dibromo-γδ-diphenyl-*n*-hexane (10 g.) and cuprous cyanide (11·3 g.) were added slowly to boiling quinoline (100 c.c.). The reaction mixture was worked up with hydrochloric acid, and the crude product recrystallised from glacial acetic acid, giving the *dicyano*-compound (4 g.), m. p. 193° (Found: N, 9·74. $C_{18}H_{20}N_2$ requires N, 9·75%).

4 : 4′-*Diamidino*-γδ-*diphenyl*-n-*hexane*.—The nitrile (2·0 g.), in chloroform solution, was converted into the imino-ether hydrochloride in the usual manner (8 days). The free iminoether base, liberated from the hydrochloride by treatment with ice and sodium hydroxide solution, gave the required *amidine isethionate* on being heated with ammonium isethionate in aqueous-alcoholic solution (Found: N, 9·56. $C_{22}H_{32}O_4N_4S_2$ requires N, 9·76%).

α-*Acetyl*-p-*bromobenzyl Cyanide* (VIII).—*p*-Bromobenzyl cyanide (25 g.) was treated with sodium (8·5 g.) in alcohol (85 c.c.). Ethyl acetate (35 c.c.) was then added all at once, and the mixture heated under reflux for 4 hours. It was then poured into water, filtered, extracted once with ether, and acidified; a red oil, which rapidly solidified, was obtained. Crystallisation from benzene gave the *acetyl* derivative (15 g.) as white, rectangular plates, m. p. 134° (Found: N, 5·9. $C_{10}H_8ONBr$ requires N, 5·9%).

3 : 4-*Dicyano*-3 : 4-*di*-(p-*bromophenyl*)-2 : 5-*diketo*-n-*hexane* (IX).—The acetyl derivative (1·0 g.) was dissolved in acetic acid (5·0 c.c.), treated with hydrogen peroxide (1 c.c., 30-vol.), and kept at 100°, the product separating from the hot solution. After cooling, a total yield of 0·6 g. was obtained, and recrystallisation from acetic acid gave the pure *compound*, m. p. 225° (Found: N, 5·9. $C_{20}H_{14}O_2N_2Br_2$ requires N, 5·9%).

p-*Cyanopropiophenonehydrazone* (XIV; R = CN).—*p*-Cyanopropiophenone (5 g.) (B.P. 488,642) was heated with hydrazine hydrate (10·0 c.c., 50% w/w solution) and alcohol (10 c.c.) for 2 hours. The *hydrazone* was isolated by precipitation with water; it was then dissolved in ether, dried (sodium sulphate), and precipitated by addition of ligroin; the unstable product (4 g.), m. p. 80—81°, had to be analysed immediately (Found: N, 23·9. $C_{16}H_{11}N_3$ requires N, 24·2%).

4 : 4′-*Dicyano*-αβ-*diethylstilbene*.—The hydrazone from 5 g. of ketone was shaken in a closed vessel with yellow mercuric oxide (8 g.) and ligroin (50 c.c.) at room temperature for 4 hours. The cherry-red solution obtained by filtration was treated with a rapid stream of sulphur dioxide at 0° to give 1·2 g. of a yellow amorphous solid; when heated to 120°, this lost sulphur dioxide, leaving a gummy mass which on trituration with ether gave crude 4 : 4′-*dicyano*-αβ-*diethylstilbene* (0·5 g.). Crystallisation from alcohol gave white needles, m. p. 216° (Found: C, 83·5; H, 6·2; N, 9·8. $C_{20}H_{18}N_2$ requires C, 84·0; H, 6·3; N, 9·8%).

p-*Bromoacetophenonehydrazone*.—*p*-Bromoacetophenone (20 g.), hydrazine hydrate (10 g., 50% w/w), and alcohol

(100 c.c.) were heated under reflux for 3 hours, then poured into water; the *hydrazone*, m. p. 164°, separated (Found: N, 13·6. $C_8H_9N_2Br$ requires N, 13·1%). In view of the known instability of hydrazones of this type, further purification was inadvisable.

p-*Cyanoacetophenonehydrazone*, m. p. 73—74°, was similarly prepared (Found: N, 26·5. $C_9H_9N_3$ requires N, 26·4%).

4 : 4′-*Diamidino-αβ-diethylstilbene*.—The nitrile (1·0 g.) was converted into the iminoether hydrochloride (5 days) in chloroform (10 c.c.) and alcohol (1·0 c.c.). The iminoether base, obtained as a white solid, m. p. 98—100°, gave the required *amidine dihydrochloride* (0·6 g.) when heated in aqueous alcohol with ammonium chloride (Found: N, 13·3; Cl, 16·46. $C_{20}H_{24}ON_2$ requires N, 13·1; Cl, 16·5%).

4 : 4′-*Dibromotolan*.—4 : 4′ : α : β-Tetrabromo-αβ-diphenylethane (10 g.) was treated with a solution of sodium (9·2 g.) in alcohol (150 c.c.), the mixture heated under reflux for ½ hour (2—3 hours for larger preparations), and poured into water. The crude tolan, m. p. 170—180°, crystallised from chloroform or dioxan, gave 5 g. of *dibromo*-compound, m. p. 182—184° (Found: Br, 47·6. $C_{14}H_8Br_2$ requires Br, 47·6%).

4 : 4′-*Dibromodeoxybenzoin* (XVIII).—4 : 4′-Dibromotolan (40 g.) was heated with concentrated sulphuric acid (200 c.c.) and acetic acid (600 c.c.) to complete solution. Vigorous mechanical agitation was essential. After cooling, the whole was diluted with water, the solid collected, dried, and recrystallised from glacial acetic acid, giving 35 g. of the *deoxybenzoin*, m. p. 137° (Found: Br, 45·1. $C_{14}H_{10}OBr_2$ requires Br, 45·2%). The *semicarbazone* had m. p. 210—212° (Found: N, 10·2. $C_{15}H_{13}ON_3Br_2$ requires N, 10·2%).

1 : 2-*Di*-(p-*bromophenyl*)-n-*propan*-2-*ol* (XX; R = H, R′ = Me).—4 : 4′-Dibromodeoxybenzoin (40 g.) was added in small portions to the Grignard solution prepared from magnesium (8·2 g.), methyl iodide (52 g.), and ether (250 c.c.) maintained at 0°. After standing overnight at room temperature, the reaction mixture was worked up with ammonium chloride. Distillation of the product, b. p. 195—200°/0·5 mm., gave the *carbinol* (32 g.) as a white solid, m. p. 62° (Found: Br, 43·1. $C_{14}H_{10}OBr_2$ requires Br, 43·3%).

4 : 4′-*Dibromo-α-methylstilbene* (XXI; R = H, R′ = Me).—The above carbinol (5 g.) was heated with anhydrous potassium hydrogen sulphate (2 g.) at 180—190° for 15 minutes. The water formed was removed in a vacuum. Extraction of the reaction mixture with boiling benzene gave 3 g. of the trans-*stilbene*, m. p. 136—137° (Found: Br, 45·4. $C_{15}H_{12}Br_2$ requires Br, 45·5%). From the mother-liquors the cis-*compound* (prisms from methyl alcohol), m. p. 73·5°, was obtained (Found: Br, 45·6%).

4 : 4′-*Dicyano-α-methylstilbene*.—4 : 4′-Dibromo-α-methylstilbene (4·8 g.), cuprous cyanide (2·7 g.), and quinoline (15 c.c.) were heated under reflux for 20 minutes. After being worked up in the usual manner and sublimed in a vacuum, 3·0 g. of crude product were obtained. Recrystallisation from glacial acetic acid gave the *dicyano*-compound (2·6 g.), m. p. 153—155° (Found: N, 11·2. $C_{17}H_{12}N_2$ requires N, 11·5%).

4 : 4′-*Diamidino-α-methylstilbene*.—The dicyano-compound (8 g.) was converted into the iminoether hydrochloride (2 days); this gave the corresponding *amidine dihydrochloride* (6 g.) on being heated for 6 hours at 45° with saturated alcoholic ammonia. It separated from dilute hydrochloric acid in pale yellow crystals (Found: N, 15·0; Cl, 19·2. $C_{17}H_{18}N_4,2HCl,H_2O$ requires N, 15·1; Cl, 19·2%).

1 : 2-*Di*-(p-*bromophenyl*)-n-*butan*-2-*ol* (XX; R = H, R′ = Et).—4 : 4′-Dibromodeoxybenzoin (50 g.) was added in portions to the cooled Grignard solution from magnesium (10·2 g.), ethyl bromide (46 g.), and ether (500 c.c.), and after being heated under reflux for 2 hours the reaction mixture was worked up with dilute sulphuric acid. Removal of the ether gave the product as an oil (54 g.) which was not distilled, as this causes partial dehydration.

4 : 4′-*Dibromo-α-ethylstilbene* (XXI; R = H, R′ = Et).—The foregoing oil (54 g.) was intimately mixed with anhydrous potassium hydrogen sulphate (24 g.), heated under 16 mm. at 190° for one hour, and the residue distilled; b. p. 190—195°/0·5 mm. 4 : 4′-Dibromostilbene (2·0 g.), m. p. 202°, was separated, and the mixture of cis- and trans-*stilbenes* redistilled; b. p. 183—185°/0·3 mm. (Found: Br, 43·7. $C_{16}H_{14}Br_2$ requires Br, 43·7%).

4 : 4′-*Dicyano-α-ethylstilbene*.—The mixed isomerides (20 g.) and cuprous cyanide (10·8 g.) were boiled in quinoline (40 c.c.) for 30 minutes. The oil which separated on pouring the reaction mixture into concentrated hydrochloric acid was extracted with chloroform, the extract washed with water, dried (sodium sulphate), and the solvent was removed; the residue distilled as a yellow oil (11 g.), b. p. 198—200°/0·4 mm. Treatment of the oil with glacial acetic acid gave 3 g. of the trans-*nitrile*, which, recrystallised from ethanol, had m. p. 126—128° (Found: N, 10·9. $C_{18}H_{14}N_2$ requires N, 10·9%). The acetic acid liquors gave 5 g. of mixed isomerides from which 2·6 g. of the pure cis-*nitrile*, m. p. 90—92°, were isolated by fractional crystallisation from glacial acetic acid and recrystallisation from ligroin (b. p. 60—80°) (Found: N, 10·9%).

trans-4 : 4′-*Diamidino-α-ethylstilbene*.—The nitrile was converted into the corresponding iminoether base in the usual manner (5 days). Treatment with ammonium chloride in aqueous alcohol gave the *amidine hydrochloride* (Found: N, 14·6; Cl, 18·5. $C_{20}H_{24}N_4,2HCl,H_2O$ requires N, 14·5; Cl, 18·5%).

4 : 4′-*Dibromo-α-methyldeoxybenzoin* (XIX; R = Me).—4 : 4′-Dibromodeoxybenzoin (52 g.) was dissolved in alcohol (75 c.c.) containing sodium (4 g.). Methyl iodide (50 g.) was added all at once. When the vigorous reaction had subsided, the mixture was heated under reflux until neutral to litmus, water was added, and the alcohol removed by distillation. Extraction of the aqueous suspension with benzene, followed by removal of the solvent and crystallisation of the residue from methanol, gave the required *product*, m. p. 69—70° (40 g.) (Found: Br, 43·4. $C_{15}H_{12}OBr_2$ requires Br, 43·5%).

2 : 3-*Di*-(p-*bromophenyl*)-n-*butan*-2-*ol* (XX; R = R′ = Me).—4 : 4′-Dibromo-α-methyldeoxybenzoin (32 g.) was added to the Grignard solution from magnesium (5·0 g.), methyl iodide (29 g.), and ether (200 c.c.), and the mixture heated under reflux for 3 hours and worked up with ice and dilute sulphuric acid. Trituration of the gummy residue with light petroleum (b. p. 40—60°) gave 22 g. of the required *carbinol*, m. p. 85—90° (Found: C, 50·0; H, 4·4; Br, 41·4. $C_{16}H_{16}OBr_2$ requires C, 50·0; H, 4·2; Br, 41·7%).

4 : 4′-*Dibromo-αβ-dimethylstilbene and* 4 : 4′ : β : γ-*Tetrabromo-βγ-diphenyl*-n-*butane*.—The above carbinol (10 g.) was heated under reflux with acetyl chloride (10 c.c.) and acetic anhydride (10 c.c.) for 4 hours. The solvents were removed by distillation at 14 mm., and the residue distilled, b. p. 190—200°/0·5 mm., giving a thick oil (8 g.) which set, on cooling, to a glass. Dehydration with potassium hydrogen sulphate gave identical results. The product was dissolved in dry chloroform (10 c.c.) and treated with bromine (3·0 g.) in chloroform (10 c.c.). Removal of the solvent and excess of bromine at room temperature gave 4 : 4′ : β : γ-tetrabromo-βγ-diphenyl-*n*-butane, m. p. 180—185° (decomp.); mixed m. p. with an authentic specimen prepared from βγ-diphenyl-*n*-butane by bromination, 182—185°. Reduction of this compound in the manner described by Barber, Slack, and Woolman (*loc. cit.*) gave *cis*-4 : 4′-dibromo-αβ-dimethylstilbene, m. p. 86° (mixed m. p. with authentic sample, 87—90°).

4 : 4′-*Dibromo-α-ethyldeoxybenzoin* (XIX; R = Et).—4 : 4′-Dibromodeoxybenzoin (202 g.) was dissolved in alcohol (400 c.c.) containing sodium (13·3 g.). Ethyl iodide (90 g.) was added, and when the initial vigorous reaction had subsided further quantities of sodium (4·9 g.) in alcohol (100 c.c.) and ethyl iodide (33·7 g.) were added. After being heated under reflux for 5 hours, the reaction mixture was poured into water and kept overnight. The light brown solid was then collected and recrystallised from a large volume of methanol, giving 200 g. of the pure *deoxybenzoin*, m. p. 52° (Found: Br, 41·65. $C_{16}H_{14}OBr_2$ requires Br, 41·7%).

3 : 4-*Di*-(p-*bromophenyl*)-n-*hexan*-3-*ol* (XX; R = R′ = Et).—The α-ethyl compound (90 g.), dissolved in dry ether (350 c.c.), was added dropwise to a Grignard solution prepared from ethyl bromide (77 g.), magnesium (17·2 g.), and dry ether (1 l.). After being heated under reflux for 3 hours, the reaction mixture was worked up with ice and dilute sulphuric acid. Removal of the ether, and then of a small amount of 4 : 4′-dibromostilbene, m. p. 203°, followed by distillation of the residue, b. p. 206—210°/0·4 mm., gave the required *carbinol* as a pale yellow glass (Found : Br, 39·0. $C_{18}H_{20}OBr_2$ requires Br, 38·8%). On standing, this deposited a crystalline compound (10 g.), apparently a solid modification of the carbinol, which can exist in a *meso*- and a racemic form. Crystallisation from ligroin (b. p. 60—80°) gave white needles, m. p. 160° (Found : Br, 38·9%).

4 : 4′-*Dibromo*-αβ-*diethylstilbene* (XXI; R = R′ = Et).—Dehydration of both forms of the above carbinol was carried out with both potassium hydrogen sulphate and acetic anhydride–acetyl chloride. In each case the same product, b. p. 200°/0·75 mm., was obtained as an almost colourless oil. On standing for many weeks, solidification slowly occurred and a solid (yield about one third of the weight of the oil) was collected and recrystallised from alcohol, forming white needles, m. p. 123° (Found : Br, 40·5. Calc. for $C_{18}H_{18}Br_2$: Br, 40·4%). The *trans*-4 : 4′-dibromodiethylstilbene described by Vargha and Kovács (*loc. cit.*) had m. p. 124°. On redistillation, the residual oil, b. p. 190—192°/0·5 mm., again deposited the same material, but much more slowly. All attempts to convert the oil into a homogeneous product by treatment with iodine in boiling nitrobenzene (to isomerise any *cis*-compound to the *trans*-form) failed.

4 : 4′-*Dicyano*-αβ-*diethylstilbene from the Dibromo-compound*.—The dibromo-compound (4·0 g.) was heated in boiling quinoline (20 c.c.) with cuprous cyanide (2·7 g.). After being worked up in the usual manner, the residual solid was sublimed repeatedly in a vacuum and finally recrystallised from ethanol, giving the dinitrile, m. p. 214—216°, identical with that previously described.

4 : 4′ : γ : δ-*Tetrabromo*-γδ-*diphenyl*-n-*hexane*.—4 : 4′-Dibromo-αβ-diethylstilbene (1·0 g.) was dissolved in dry chloroform (5 c.c.) and treated with bromine (0·6 g.) in chloroform (5 c.c.). Uptake of bromine was almost immediate in daylight, and removal of the solvent and excess of bromine at room temperature gave the *tetrabromo*-compound, m. p. 170° (decomp.) after recrystallisation from a very large volume of glacial acetic acid (Found : Br, 55·8. $C_{18}H_{10}Br_4$ requires Br, 55·8%).

4 : 4′-*Dibromo*-α-*benzyldeoxybenzoin*.—4 : 4′-Dibromodeoxybenzoin (10 g.) was dissolved in alcohol (12 c.c.) containing sodium (0·7 g.). Benzyl chloride (8·9 g.) was added, and when the initial reaction had subsided, this was followed by alcohol (4 c.c.) containing sodium (0·25 g.). Further benzyl chloride (3·3 g.) was then added and refluxing continued to neutrality. The reaction mixture was then poured into water, and the alcohol removed by distillation. Recrystallisation of the residue from alcohol gave the *product* (6·5 g.), m. p. 100—102° (Found : Br, 35·6. $C_{21}H_{16}OBr_2$ requires Br, 36·0%).

The authors wish to express their thanks to Mr. S. Bance for the semi-microanalyses, to Miss P. Z. Gregory for help with some of the preparations, to Dr. A. J. Ewins, F.R.S., for his continued interest, and to the Directors of Messrs. May & Baker, Limited, for permission to publish these results.

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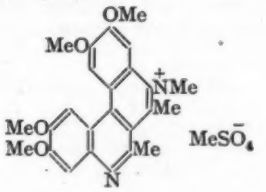
167. *Attempts to find New Antimalarials. Part XXI.*

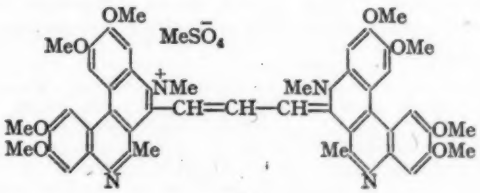
By M. J. S. DEWAR.

The present investigation was undertaken with the object of testing the antimalarial properties of derivatives of heterocyclic ring systems hitherto untried in this connexion. A number of amines derived from pyrroquinolines, diveratrocopyrine, pyrazole, phenylpyrazole, and tetrazolopyrimidine have been prepared and are being tested for antimalarial and general pharmacological activity : some quaternary salts were also made with a view to possible trypanocidal action.

DERIVATIVES of diveratrocopyrine were obtained by Lawson, Perkin, and Robinson (J., 1924, **125**, 640) by condensing β-diketones and related compounds with diaminoveratrone; the process is a double Friedländer synthesis. From the dimethyldiveratrocopyrine already described, a *methosulphate* (I) was prepared, and by the action of ethyl orthoformate in boiling pyridine this was converted into *dimethyldiveratrocopyrocyanine* (II) (M, 906). In order to introduce a basic side chain into the copyrine nucleus, 7-*diethylaminoheptane*-2 : 4-*dione* (III) was prepared by a Claisen condensation of 5-diethylaminopentan-2-one and ethyl acetate, and this intermediate was condensed with diaminoveratrone, affording a good yield of *methyl*-γ-*diethylaminopropyldiveratrocopyrine* (IV).



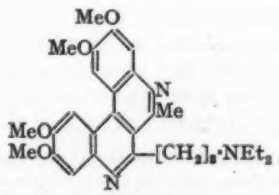
(I.)



(II.)

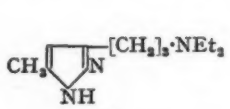
$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}[CH_2]_3{\cdot}NEt_2$

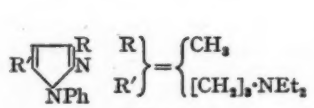
(III.)

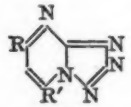


(IV.)

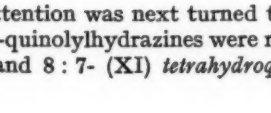
The same useful intermediate (III) was next employed in the preparation of several heterocyclic amines. From (III) and hydrazine, 5-*methyl*-3-(*γ-diethylaminopropyl*)*pyrazole* (V) was obtained, and phenylhydrazine gave the corresponding *phenylpyrazole*, probably as a mixture of isomerides (VI), since no crystalline derivative could be obtained. Finally *C*-aminotetrazole with (III) gave a similar mixture of methyl-*γ*-diethylaminopropyltetrazolopyrimidines (VII), one isomeride of unknown structure being isolated as its crystalline *picrate*.

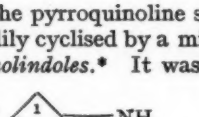

(V.)

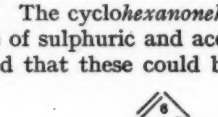

(VI.)

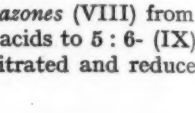

(VII.)

Attention was next turned to the pyrroquinoline series. The cyclo*hexanonehydrazones* (VIII) from 5-, 6-, and 8-quinolylhydrazines were readily cyclised by a mixture of sulphuric and acetic acids to 5 : 6- (IX), 6 : 5- (X), and 8 : 7- (XI) *tetrahydroquinolindoles*.* It was hoped that these could be nitrated and reduced, and


(VIII.)

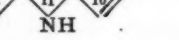

(IX.)


(X.)

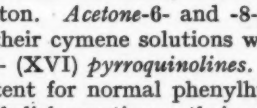

(XI.)

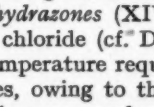
the resulting amines then condensed with suitable chloroalkylamines; but when (IX) or (X) was treated with potassium nitrate in sulphuric acid at — 15° (cf. Perkin and Plant, J., 1921, **119**, 1825), analysis showed that the unstable products were actually 13-*nitro*-12-*hydroxy*-1 : 2 : 3 : 4 : 12 : 13-*hexahydro*-5 : 6- (XII) and -6 : 5- (XIII) *quinolindoles*, formed by addition of nitric acid to the indole double bond. Such addition was observed by Perkin and Plant when tetrahydrocarbazole was treated with nitric acid in acetic acid, but that it should take place in concentrated sulphuric acid is very surprising. The occurrence of this abnormal reaction doubtless manifests the well-known deactivating influence of a pyridine ring.

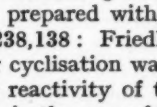
(XII.)


(XIII.)

A second line of approach was more successful. Kühn and Stein (*Ber.*, 1937, **70**, 567) synthesised gramine and two other dialkylaminomethylindoles by condensing indole with formaldehyde and secondary amines; this reaction has not been extended, but it promised a good method for introducing basic groups into the pyrroquinoline skeleton. *Acetone*-6- and -8-*quinolylhydrazones* (XIV) were prepared without difficulty, and cyclised by boiling their cymene solutions with zinc chloride (cf. D.R.-P. 238,138: Friedländer, **10**, 333) to 6 : 5- (XV) and 8 : 7- (XVI) *pyrroquinolines*. The temperature required for cyclisation was higher than that described in the patent for normal phenylhydrazones, owing to the lesser reactivity of the quinoline ring. The products gave Ehrlich reactions; their acid solutions were coloured and, in the case of (XVI), fluorescent. In the Fischer synthesis of (XVI) a stable zinc complex was formed and prolonged boiling with alkali was necessary to liberate the free base; also (XVI) was far more volatile than (XV), indicating hydrogen bonding between the nitrogens. These results, showing the ease of chelation between the nitrogen atoms, are interesting in view of certain theories of antiplasmodial action; a similar arrangement of atoms is present in the plasmoquine molecule.


(XIV.)

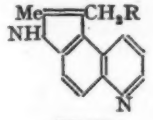

(XV.)


(XVI.)

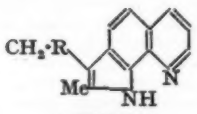
The action of formaldehyde and secondary amines on (XV) and (XVI) in acetic acid furnished a series of 2-*methyl*-3-*dialkylaminomethyl*-6 : 5- (XVII) and -8 : 7-*pyrroquinolines* (XVIII). The amines used were diethylamine, dibutylamine, piperidine, morpholine, and tetrahydro*iso*quinoline. The crude yields were almost theoretical, but some loss occurred in purification which was usually effected by way of the oxalates. The 6 : 5-series gave intense colorations in hot sulphuric acid; it is interesting that the compound from

* The name quinolindole is proposed for the ring systems formed by fusion of quinoline with indole *via* its α- and β-positions; the numbers indicate the position of the attachment first of the α- and then of the β-position of indole to the quinoline system, and the final ring systems are numbered by analogy with carbazole.

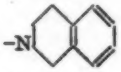
piperidine gave a beautiful green colour while the others all gave shades of red. Salts of the 8 : 7-series were fluorescent in solution.



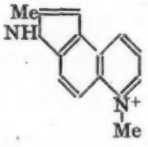
(XVII.)

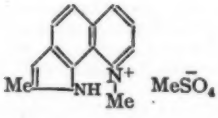


(XVIII.)

R = NEt_2, NBu_2, , , 

Finally an attempt was made to convert (XV) into an analogue of Fischer's base by treating it with an excess of methyl iodide in methanol under pressure. However, the product, formed in theoretical yield, was the *methiodide* (XIX) of (XV), complete inactivation of the indole ring being enforced by the positive charge at the other end of the molecule. In confirmation no colour was developed by (XIX) on heating with Ehrlich's reagent, a curious contrast to the behaviour of the *methosulphate* (XX) of (XVI), which gave a normal Ehrlich reaction.

(XIX.) 

(XX.) 

Experimental.

(All salts were dried in a high vacuum at 60° for analysis; all were hygroscopic.)

Dimethyldiveratrocopyrine Methosulphate (I).—A mixture of dimethyldiveratrocopyrine (4·33 g.) (Lawson, Perkin, and Robinson, *loc. cit.*), methyl sulphate (2·5 g.), and toluene (150 c.c.) was boiled for 6 hours under reflux, cooled, and the *methosulphate* collected; it crystallised from 90% alcohol in greenish-yellow needles (4·15 g., 72%), m. p. 250° (decomp.) (Found: C, 56·9; H, 5·5; S, 6·4. $C_{24}H_{28}O_8N_2S$ requires C, 57·1; H, 5·6; S, 6·3%). The red solution of the compound had an intense green fluorescence.

Dimethyldiveratrocopyrocyanine (II).—A mixture of the methosulphate (2 g.), ethyl orthoformate (1·18 g.), and dry pyridine (20 c.c.) was boiled for 5 hours under reflux, and when cold the *cyanine* (1·48 g., 88%) was precipitated with ethyl acetate. It crystallised from alcohol in mauve-black needles with a green lustre, m. p. 205° (Found: C, 62·9; H, 6·1; S, 3·0. $C_{46}H_{50}O_{12}N_4S,C_2H_6O$ requires C, 63·0; H, 5·9; S, 3·4%). Solutions of the compound showed an extraordinary dichroism, being crimson in bulk, blue-green in thin layers. The absorption spectrum, of normal cyanine type, showed maxima at 5600° A. (log ε = 3·45) and 6100 A. (log ε = 3·55).

7-Diethylaminoheptan-2 : 4-dione.—A suspension of sodium ethoxide (from 12·5 g. of sodium), in a mixture of toluene (125 c.c.) and dry ethyl acetate (150 c.c.), was stirred mechanically and cooled below 5° while 5-diethylaminopentan-2-one (78·5 g.) was gradually added. After 2 hours, the cooling bath was removed, and next day acetic acid (30 g.) and ether (500 c.c.) were added, the solution filtered and evaporated on a steam-bath, and the residual oil fractionated. Unchanged ketone (40 g.) distilled at 90—100°/30 mm., and then the *diketone* (34·3 g., 34%, or 70% allowing for recovery) was collected at 140—145°/30 mm.; it redistilled as a colourless oil, b. p. 139—140°/28 mm., $n_D^{20°}$ 1·6529 (Found: C, 66·4; H, 10·5; N, 6·9. $C_{11}H_{21}O_2N$ requires C, 66·3; H, 10·5; N, 7·0%). The compound was miscible with water and gave an intense cherry-red colour with aqueous or alcoholic ferric chloride.

Methyl-γ-diethylaminopropyldiveratrocopyrine (IV).—A solution of diaminoveratrone (5 g.) (Lawson, Perkin, and Robinson, *loc. cit.*) and diethylaminoheptanedione (5 g.) in acetic acid (25 c.c.) was boiled for 2 hours under reflux, diluted with water, basified with ammonia, filtered, and the *copyrine* then precipitated with sodium hydroxide, taken up in chloroform, dried over potassium carbonate, passed through an alumina column, recovered by evaporation, and converted into the *oxalate*, which crystallised from alcohol in orange rosettes (6·4 g.), m. p. 125° with gas evolution (Found: C, 54·1; H, 6·3; N, 5·9. $C_{28}H_{35}O_4N_3,2C_2H_2O_4,3H_2O$ requires C, 54·0; H, 6·3; N, 5·9%). The free *base* crystallised from ethyl acetate and light petroleum in cream-coloured needles, m. p. 148—149°, which were dried at 100°/0·01 mm. for analysis (Found: C, 70·0; H, 7·4; N, 9·0. $C_{28}H_{35}O_4N_3$ requires C, 70·4; H, 7·3; N, 8·8%). The *hydrochloride* crystallised from alcohol in microscopic saffron needles with no definite m. p. (Found: C, 59·2; H, 6·9; N, 7·4. $C_{28}H_{35}O_4N_3,2HCl,H_2O$ requires C, 59·1; H, 6·9; N, 7·4%).

5-Methyl-3-(γ-diethylaminopropyl)pyrazole (V).—A solution of hydrazine hydrate (1·25 g.) in alcohol (5 c.c.) was added to one of diethylaminoheptanedione (5 g.) in alcohol (10 c.c.), and the whole boiled for 1 hour under reflux. After distillation of the solvent, the *pyrazole* was converted in ether and acetone into its deliquescent *hydrochloride*, which crystallised on addition of absolute ether to its solution in absolute alcohol in colourless, acicular plates (6·15 g.), m. p. 210° (decomp.) (Found: C, 48·9; H, 8·5; N, 15·4. $C_{11}H_{21}N_3,2HCl$ requires C, 49·2; H, 8·6; N, 15·7%). The compound appeared to form a complex with Fehling's solution, which it did not reduce.

1-Phenyl-3 (or *5*)*-methyl-5* (or *3*)*-(γ-diethylaminopropyl)pyrazole* (VI).—A solution of phenylhydrazine (3·91 g.) and diethylaminoheptanedione (7·20 g.) in alcohol (30 c.c.) was boiled under reflux for 2½ hours, the solvent distilled, and the residue fractionated. The *pyrazole* (7·52 g., 77%) was collected at 141—142°/0·15 mm. as a pale yellow oil with a faint basic smell, $n_D^{20°}$ 1·5400 (Found: C, 75·0; H, 9·4; N, 15·6. $C_{17}H_{25}N_3$ requires C, 75·2; H, 9·2; N, 15·5%). No derivative would crystallise; the *hydrochloride* was a gum (Found, in material dried in a vacuum over potassium hydroxide at room temperature: N, 10·3. $C_{17}H_{25}N_3,2HCl,1\frac{1}{2}C_2H_6O$ requires N, 10·2%).

4 (or *6*)*-Methyl-6* (or *4*)*-(γ-diethylaminopropyl)-1 : 2-(1′ : 5′-tetrazolo)pyrimidine* (VII).—A mixture of aminotetrazole (3·4 g.), diethylaminoheptanedione (7·96 g.), alcohol (60 c.c.), and piperidine (4 drops) was refluxed for 60 hours, and the clear solution poured into one of picric acid (20 g.) in hot alcohol (2 l.). The *picrate* (12·5 g., 65%) after recrystallisation from alcohol had m. p. 105—120° (Found: C, 45·2; H, 4·8; N, 26·4. $C_{13}H_{20}N_6,C_6H_3O_7N_3$ requires C, 45·3; H, 4·8; N, 26·4%). By separating and crystallising from alcohol the last crop of crystals, one isomeric *picrate* was obtained pure in small canary-yellow prisms, m. p. 145—146° (Found: C, 46·0; H, 5·6. $C_{13}H_{20}N_6,C_6H_3O_7N_3,C_2H_6O$ requires C, 45·9; H, 5·5%).

cyclo*Hexanone-6-quinolylhydrazone.*—To a solution of 6-quinolylhydrazine dihydrochloride (19·4 g.), sodium acetate (12 g. of hydrate), and alcohol (50 c.c.) in water (150 c.c.) was added one of *cyclo*hexanone (8·2 g.) in alcohol (20 c.c.),

and the whole heated for 1 hour on a steam-bath. When cold, the *hydrazone* was collected; it crystallised from ethyl acetate in glistening, yellow, rectangular plates (9 g.), m. p. 180° (Found: C, 75·6; H, 7·3; N, 17·5. $C_{15}H_{17}N_3$ requires C, 75·3; H, 7·1; N, 17·6%).

1 : 2 : 3 : 4-*Tetrahydro*-6 : 5-*quinolindole* (X).—A solution of crude hydrazone (18·7 g.) and sulphuric acid (6 c.c.) in acetic acid (100 c.) was heated for 10 minutes on a steam-bath, then cooled, and the orange sulphate collected. The free *quinolindole* was liberated with ammonia and crystallised from acetone in large polyhedra (14·4 g., 72%), m. p. 201—202° (Found: C, 80·6; H, 6·5; N, 12·8. $C_{15}H_{14}N_2$ requires C, 81·1; H, 6·3; N, 12·6%).

cyclo*Hexanone*-5-*quinolylhydrazone*.—Prepared as before from 5-quinolylhydrazine dihydrochloride (23·7 g.), the *hydrazone* (20·6 g.; 92%) crystallised from carbon tetrachloride in bright orange needles, m. p. 131°, which were dried at 60°/0·01 mm. for analysis (Found: C, 65·0; H, 6·1; N, 15·2. $C_{15}H_{17}N_3,\frac{1}{4}CCl_4$ requires C, 65·8; H, 6·1; N, 15·1%). Drying at 100° led to decomposition.

1 : 2 : 3 : 4-*Tetrahydro*-5 : 6-*quinolindole* (IX).—Prepared as before from the hydrazone (9·1 g.) and sulphuric acid (3 c.c.) in acetic acid (50 c.c.), the *quinolindole* (7·58 g., 89%) crystallised from pyridine in microscopic rectangular plates, m. p. 286—288° (Found: C, 80·8; H, 6·1; N, 12·8%). The compound was very sparingly soluble in all solvents except acids or hot pyridine.

1 : 2 : 3 : 4-*Tetrahydro*-8 : 7-*quinolindole* (XI).—Prepared without isolation of the intermediate hydrazone, the *quinolindole* crystallised from ethyl acetate, with alumina treatment, in large trapezoidal tablets, m. p. 151° (Found: C, 80·9; H, 6·1; N, 12·8%).

13-*Nitro*-12-*hydroxy*-1 : 2 : 3 : 4 : 12 : 13-*hexahydro*-6 : 5-*quinolindole* (XIII).—To a solution of the tetrahydroquinolindole (0·74 g.) in sulphuric acid (5 c.c.) cooled below −15° was added gradually with stirring powdered potassium nitrate (0·35 g.). After 5 minutes the solution was poured on ice, immediately basified with ammonia, and the *nitro-compound* (0·77 g., 81%) rapidly collected, washed with cold water and dried in a vacuum over sodium hydroxide. It was unstable to acids, bases, or hot solvents, but crystallised with heavy loss from methyl ethyl ketone and light petroleum in buff needles, m. p. 169° (decomp.) (Found: C, 63·4; H, 4·8; N, 14·8. $C_{15}H_{15}O_3N_3$ requires C, 63·1; H, 5·3; N, 14·7%).

13-*Nitro*-12-*hydroxy*-1 : 2 : 3 : 4 : 12 : 13-*hexahydro*-5 : 6-*quinolindole* (XII).—Prepared similarly, this *nitro-compound* was obtained as an unstable yellow powder which could not be recrystallised (Found: N, 14·6%).

Acetone-6-*quinolylhydrazone*.—The hydrazine dihydrochloride prepared from 6-aminoquinoline (14·4 g.) (Wieland and Horner, *Annalen*, 1938, **536**, 92) was dissolved in water (100 c.c.) containing acetone (10 c.c.), a solution of sodium acetate (100 g. of hydrate) in water (150 c.c.) added, and the whole warmed to 50° for 15 minutes. When cold, the *hydrazone* was collected and crystallised from dilute alcohol, forming pale yellow plates (14·5 g., 73%), m. p. 163—164° (Found: C, 71·0; H, 6·4; N, 20·9. $C_{12}H_{13}N_3,\frac{1}{4}H_2O$ requires C, 70·8; H, 6·6; N, 20·6%).

2-*Methyl*-6 : 5-(2′ : 3′-*pyrro*)*quinoline* (XV).—A mixture of the hydrazone (3·6 g.), powdered zinc chloride (4 g.), and cymene (16 c.c.) was heated under reflux in a bath at 175—180° for 3 hours. The solid product was washed with light petroleum, dried, powdered, and stirred into N-hydrochloric acid (100 c.c.), and after a few minutes the resulting suspension was poured into sodium hydroxide solution (200 c.c. of 25%). The *pyrroquinoline* was collected, and crystallised from chloroform and light petroleum in rhombs (2·83 g., 86%), m. p. 198°; it was freed from solvent for analysis by sublimation at 200°/0·5 mm. (Found: C, 78·9; H, 5·8; N, 15·9. $C_{12}H_{10}N_2$ requires C, 79·1; H, 5·5; N, 15·4%). The compound gave a scarlet colour with hot Ehrlich's reagent, fading reversibly to orange on cooling, and an amethyst solution in hot sulphuric acid.

2-*Methyl*-3-*diethylaminomethyl*-6 : 5-*pyrroquinoline* (XVII; R = NEt_2).—To a solution of the methylpyrroquinoline (0·91 g.) and diethylamine (0·37 g.) in acetic acid was added formalin (0·4 c.c. of 36·9%). Next day water was added, the solution basified, and excess diethylamine steam-distilled under reduced pressure. The methyldiethylaminomethylpyrroquinoline was then extracted with chloroform, and the chloroform solution dried over potassium carbonate, passed through an alumina column, and evaporated. The residual base was converted into its *oxalate*, which crystallised from alcohol in orange-yellow needles (2·04 g., 94%), m. p. 166° with gas-evolution (Found: C, 54·6; H, 5·7; N, 9·0. $C_{17}H_{21}N_3,2C_2H_2O_4,H_2O$ requires C, 54·2; H, 5·8; N, 9·0%). The very soluble free base had m. p. 125—130°; it was converted in ether into the *hydrochloride*, which crystallised from alcohol–ethyl acetate in microscopic lemon-yellow prisms, m. p. 202—203° (Found: C, 58·9; H, 7·6; N, 10·7. $C_{17}H_{21}N_3,2HCl,C_2H_6O$ requires C, 59·0; H, 7·5; N, 10·9%). Solutions in hot sulphuric acid were burgundy-red.

2-*Methyl*-3-*dibutylaminomethyl*-6 : 5-*pyrroquinoline* (XVII; R = NBu_2).—Prepared similarly, the *oxalate* crystallised from moist alcohol in chrome-yellow needles, m. p. 205° with gas-evolution (Found: C, 58·0; H, 6·8; N, 7·9. $C_{21}H_{29}N_3,2C_2H_2O_4,H_2O$ requires C, 57·7; H, 6·7; N, 8·1%). The *hydrochloride* crystallised from alcohol–ethyl acetate in deliquescent, chrome-yellow needles, m. p. 171° (Found: C, 61·1; H, 7·9; N, 10·5. $C_{21}H_{29}N_3,2HCl,H_2O$ requires C, 60·9; H, 8·0; N, 10·1%). The sulphuric acid colour resembled that of the diethyl analogue.

2-*Methyl*-3-*piperidinomethyl*-6 : 5-*pyrroquinoline*.—In this case the *base* crystallised from acetone in ochre rosettes, m. p. 228° (Found, in material dried at 100°/0·01 mm.: C, 77·2; H, 7·2; N, 14·9. $C_{18}H_{21}N_3$ requires C, 77·4; H, 7·5; N, 15·1%). The *hydrochloride* crystallised from 95% alcohol in long, bright yellow, radiating needles, m. p. 232° (Found: loss in weight at 60°/0·01 mm., 6·9. $C_{18}H_{21}N_3,2HCl,2H_2O$ requires $1\frac{1}{2}H_2O$, 6·2%. Found, in dried material: C, 59·2; H, 6·7; N, 11·4. $C_{18}H_{21}N_3,2HCl,\frac{3}{2}H_2O$ requires C, 59·3; H, 6·7; N, 11·5%). The solution in hot sulphuric acid was leaf-green.

2-*Methyl*-3-*morpholinomethyl*-6 : 5-*pyrroquinoline*.—The *base* crystallised from acetone in cream-coloured prisms, m. p. 228°, which were dried at 100°/0·01 mm. for analysis (Found: C, 72·4; H, 6·9; N, 14·6. $C_{17}H_{19}ON_3$ requires C, 72·6; H, 6·8; N, 14·9%). The *hydrochloride* crystallised from 90% alcohol in long, yellow needles, m. p. 230° (Found: C, 55·1; H, 6·5; N, 11·0. $C_{17}H_{19}ON_3,2HCl,H_2O$ requires C, 54·8; H, 6·2; N, 11·3%). The solution in hot sulphuric acid was cherry-red.

2-*Methyl*-3-*tetrahydro*isoquinolyl-6 : 5-*pyrroquinoline*.—The base, m. p. 199—204°, was purified by extracting its almost insoluble picrate with boiling alcohol and converted into its *hydrochloride*, which crystallised from alcohol in chrome-yellow rosettes, m. p. 196° (Found: C, 65·0; H, 6·2; N, 10·2. $C_{22}H_{21}N_3,2HCl,\frac{1}{2}C_2H_6O$ requires C, 65·2; H, 6·2; N, 9·9%). The solution in hot sulphuric acid was burgundy-red by transmitted, green by reflected light.

2-*Methyl*-6 : 5-*pyrroquinoline Methiodide* (XIX).—A mixture of the pyrroquinoline (1·4 g.), methyl iodide (5·5 g.), quinol (0·1 g.), and methanol (3 c.c.) was heated for 10 hours in a sealed tube at 130°, and the orange-red, crystalline solid (2·7 g., 100%) washed out with ether and recrystallised from aqueous alcohol, forming bright orange-red rosettes, m. p. 290° (decomp.) (Found: C, 49·0; H, 4·7; N, 8·3. $C_{13}H_{12}N_2I,\frac{1}{2}C_2H_6O$ requires C, 48·4; H, 4·6; N, 8·1%). The compound gave no colour with Ehrlich's reagent.

Acetone-8-*quinolylhydrazone*.—Prepared as for its isomer but from 8-aminoquinoline (44 g.), the *hydrazone* crystallised from dilute alcohol in large, pale yellow, rhombic plates (42·1 g., 69%), m. p. 70—71° (Found: C, 71·4; H, 6·7; N, 19·6. $C_{12}H_{13}N_3,\frac{1}{4}C_2H_6O$ requires C, 71·3; H, 6·9; N, 20·0%).

2-*Methyl*-8 : 7-*pyrroquinoline*.—A mixture of the hydrazone (6·1 g.), powdered zinc chloride (6 g.), and cymene c.c.) was heated under reflux in a bath at 175—180° for 5 hours. When cold, the solid was washed with light petro-

leum, powdered, and heated for 4 hours on a steam-bath with sodium hydroxide solution (200 c.c. of 20%), cooled, and the *pyrroquinoline* collected and crystallised from aqueous alcohol (charcoal), affording pale yellow, spear-shaped plates (3·78 g., 67%), m. p. 155—157°; it was freed from solvent for analysis by sublimation at 150°/0·01 mm. (Found: C, 78·8; H, 5·3; N, 15·1. $C_{12}H_{10}N_2$ requires C, 79·1; H, 5·5; N, 15·4%). With hot Ehrlich's reagent the compound gave a cherry-red colour, fading reversibly to orange on cooling. Compounds of this series all gave brown solutions in hot sulphuric acid, showing a green fluorescence; and solutions of their salts fluoresced markedly. The derivatives were prepared as for the 6 : 5-analogues.

2-*Methyl*-3-*diethylaminomethyl*-8 : 7-*pyrroquinoline*.—The *oxalate* crystallised from aqueous alcohol in pale yellow rosettes, m. p. 184° with gas-evolution (Found: C, 56·3; H, 5·5; N, 9·8. $C_{17}H_{21}N_3,2C_2H_2O_4$ requires C, 56·4; H, 5·6; N, 9·4%). The *hydrochloride* crystallised from 95% alcohol in golden, bladed plates, m. p. 202° with gas-evolution (Found: C, 58·5; H, 7·0; N, 12·4. $C_{17}H_{21}N_3,2HCl,\frac{1}{2}H_2O$ requires C, 58·5; H, 6·9; N, 12·0%).

2-*Methyl*-3-*dibutylaminomethyl*-6 : 5-*pyrroquinoline*.—The *oxalate* crystallised from alcohol in saffron rosettes, m. p. 167° with gas-evolution (Found: C, 59·5; H, 6·7; N, 8·6. $C_{21}H_{29}N_3,2C_2H_2O_4$ requires C, 59·6; H, 6·6; N, 8·4%). The *hydrochloride* crystallised from ethyl acetate containing a little alcohol in pale yellow rosettes, m. p. 135—136° (Found: loss in weight at 60°/0·01 mm., 5·5. $C_{21}H_{29}N_3,2HCl,2H_2O$ requires $1\frac{1}{2}H_2O$, 6·2%. Found, in dried material: C, 62·0; H, 7·6; N, 10·4. $C_{21}H_{29}N_3,2HCl,\frac{1}{2}H_2O$ requires C, 62·2; H, 7·9; N, 10·4%).

2-*Methyl*-3-*piperidinomethyl*-8 : 7-*pyrroquinoline*.—The *oxalate* crystallised from moist alcohol in canary-yellow rosettes, m. p. 135° with gas-evolution (Found: C, 57·1; H, 6·2; N, 8·6. $C_{18}H_{21}N_3,2C_2H_2O_4,C_2H_6O$ requires C, 57·0; H, 6·1; N, 8·3%). The *hydrochloride* crystallised from aqueous alcohol in saffron needles, m. p. 142° with gas-evolution (Found: loss in weight at 60°/0·01 mm., 7·4. $C_{18}H_{21}N_3,2HCl,2H_2O$ requires $1\frac{1}{2}H_2O$, 7·7%. Found, in dried material: C, 60·2; H, 6·6; N, 11·9. $C_{18}H_{21}N_3,2HCl,\frac{1}{2}H_2O$ requires C, 60·3; H, 6·6; N, 11·7%).

2-*Methyl*-3-*morpholinomethyl*-8 : 7-*pyrroquinoline*.—The *oxalate* crystallised from aqueous alcohol in fawn-yellow prisms, m. p. 155—156° with gas-evolution (Found: C, 56·4; H, 5·8; N, 8·8. $C_{17}H_{19}ON_3,2C_2H_2O_4,C_2H_6O$ requires C, 56·7; H, 6·0; N, 8·6%). The *hydrochloride* crystallised from moist alcohol in feathery, saffron needles, m. p. 228° (decomp.) (Found: loss in weight at 60°/0·01 mm., 4·2. $C_{17}H_{19}ON_3,2HCl,H_2O$ requires $\frac{1}{2}H_2O$, 3·6%. Found, in dried material: C, 56·8; H, 6·2; N, 11·5. $C_{17}H_{19}ON_3,2HCl,\frac{1}{2}H_2O$ requires C, 56·9; H, 6·0; N, 11·7%).

2-*Methyl*-3-*tetrahydroisoquinolyl*-8 : 7-*pyrroquinoline*.—The *hydrochloride* crystallised with difficulty from absolute alcohol on addition of dry ether in microscopic yellow needles, m. p. 85° (Found: loss in weight at 60°/0·01 mm., 7·9. $C_{22}H_{21}N_3,2HCl,3H_2O$ requires $2H_2O$, 7·9%. Found, in dried material: C, 63·3; H, 5·9; N, 9·7. $C_{22}H_{21}N_3,2HCl,H_2O$ requires C, 63·2; H, 6·0; N, 10·0%).

2-*Methyl*-8 : 7-*pyrroquinoline Methosulphate* (XX).—A solution of the methylpyrroquinoline (1·84 g.) and methyl sulphate (1·6 g.) in benzene (20 c.c.) was boiled for 3 hours under reflux; the *methosulphate* which separated crystallised from alcohol and ethyl acetate in long, orange-brown prisms, m. p. 157°; these were dried in a vacuum at room temperature over phosphoric oxide for analysis (Found: C, 54·7; H, 5·6; S, 10·0. $C_{14}H_{16}O_4N_4S,\frac{1}{4}C_2H_6O$ requires C, 54·5; H, 5·5; S, 10·0%). The deep red solutions of this quaternary salt had an intense green fluorescence, and with hot Ehrlich's reagent it gave a scarlet colour, fading reversibly to flame-red on cooling.

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DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, August 5th*, 1944.]

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168. *Attempts to find New Antimalarials. Part XXII.*

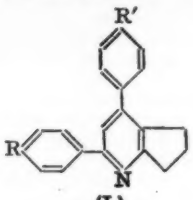
By M. J. S. DEWAR.

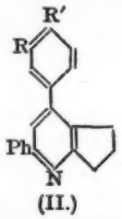
In continuation of the programme outlined in Part XXI, attention has been directed to the diphenylazahydrindene series of compounds, the synthetic procedure of Stobbe and Volhard (*Ber.*, 1902, **35**, 3973) being used. In this connexion a new method of diethylaminoethylation of amines has been devised by using the Eisleb reaction; this has also been applied to harmine. Finally, unsuccessful attempts to prepare the quinazoline analogue of plasmoquine and sulphanilamido-derivatives of quinazoline are described, and also some new methods for synthesising quinazolines.

STOBBE and VOLHARD (*loc. cit.*) describe a synthesis of 5 : 7-diphenyl-4-azahydrindene derivatives by Michael addition of *cyclo*pentanone to the double bond of chalkones, followed by ring closure of the diketone with hydroxylamine hydrochloride. This method has been used to make the *methiodides*, (I; R, R′ = H) and (I; R = H, R′ = OMe), respectively, also (I; R = H; R′ = NMe_2), (I; R = NHAc, R′ = NMe_2), and (II; R = NO_2, R′ = H) and (II; R = H, R′ = NO_2), respectively. Catalytic reduction of the nitro-compounds over Raney nickel gave the corresponding *amines*, which were converted in the usual manner by way of their *p-acetamidobenzenesulphonyl* derivatives into the *sulphanilamide* derivatives (II; R = *p*-NH_2·C_6H_4·SO_2·NH, R′ = H and *vice versa*). In the syntheses the yields were extremely good with the nitrochalkones, moderate with chalkone itself, and poor with the other chalkones. The intermediate diketones were not as a rule isolated, as they could not be crystallised. In the preparation of (I; R = H, R′ = OMe) much gum was formed and the yield of quaternary salt was poor; perhaps demethylation took place, as with 4-methoxypyridine.

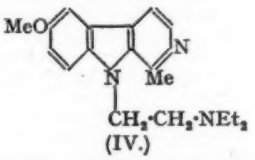
The next objective was the aminoalkylation of the amines (II; R = NH_2, R′ = H) and (II; R = H, R′ = NH_2). The conventional method, by heating the free amine with a chloroalkylamine hydrochloride, was not attractive, because the high molecular weight of these products would make the usual purification by distillation impossible. Eisleb has described a method of diethylaminoethylating active methylene groups (*Ber.*, 1941, **74**, 1433) by means of sodamide and chloroethyldiethylamine in boiling toluene; under these conditions the chloride is, surprisingly enough, not attacked by sodamide and good yields of the desired products are obtained. Eisleb also used the same process successfully to *N*-alkylate diphenylamine, carbazole, 2-methylindole, and acridone, but did not extend it to simpler amines. When aniline and methylaniline were treated with sodamide and chloroethyldiethylamine in toluene, excellent yields of diethylaminoethylaniline (III;

R = H) and diethylaminoethylmethylaniline (III; R = Me) were obtained; crystalline derivatives of these compounds were prepared for the first time.


(I.)

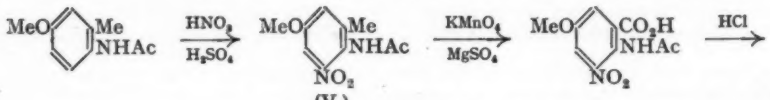

(II.)

$Ph\cdot NR\cdot CH_2\cdot CH_2\cdot NEt_2$ (III.)


(IV.)

The same process applied to harmine gave 9-*diethylaminoethylharmine* (IV), whereas the two amines of type (II) were smoothly converted into the corresponding 5-*phenyl*-7-(β-*diethylaminoethylaminophenyl*)-4-*azahydrindenes* (II; R = $NH_2\cdot CH_2\cdot CH_2\cdot NEt_2$, R′ = H, and vice versa), in 74% and 86% yields respectively. In the former case the chloride hydrochloride method was actually tried and by it a 20% yield of an impure oxalate of (II; R = $NH\cdot CH_2\cdot CH_2\cdot NEt_2$, R′ = H) was obtained. In these cases, *N*-alkylation would be expected to occur much more readily than *C*-alkylation of the methylene groups attached to the α-position of the pyridine ring. There is little doubt that the formulation of the products is correct. Moreover, neither of the alkylated pyridine derivatives could be diazotised, in contrast to their parent amines.

In an unsuccessful attempt to synthesise the quinazoline analogue of plasmoquine, 4-*chloro*-8-*nitro*-6-*methoxyquinazoline* (VII; R = Cl) was prepared by the following reactions: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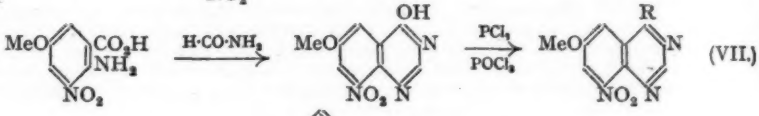
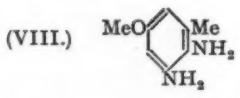
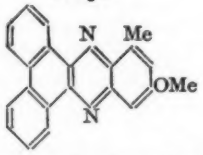

(VII.)

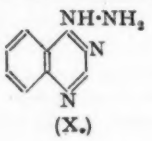

(VIII.)

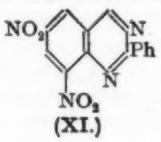

(IX.)

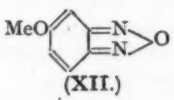
The orientation of (V) was established by hydrolysis to 3-*nitro*-5-*methoxy*-o-*toluidine*, followed by reduction to the diamine (VIII) and condensation with phenanthraquinone to 10-*methyl*-12-*methoxyphenanthrazine* (IX). Solutions of (IX) in benzene showed a typical though weak fluorescence, and with sulphuric acid it gave an intense violet colour. The deep colour of (VI) and 3-nitro-5-methoxy-*o*-toluidine, in contrast to their pale acetyl derivatives, confirmed the *o*-nitroaniline structure.

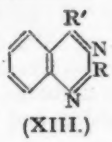
Another possible route to (VI), by nitration of acetyl-5-methoxyanthranilic acid, was abandoned when the methylation of 4-hydroxyazobenzene-2-carboxylic acid proved unexpectedly difficult, although some 4-*methoxyazobenzene*-2-*carboxylic acid* was eventually obtained. It was, moreover, realised from analogy with aceto-2-nitroanisidide (which is nitrated ortho to the nitro-group) that nitration of the acetylanthranilic acid might occur in the 6-position.

As a model for the reduction of (VII; R = Cl), 4-chloroquinazoline was investigated. Catalytic reduction over palladised charcoal gave exclusively dihydroquinazoline; chemical reduction or reduction in hydroxylic solvents gave only 4-quinazolone or its derivatives. With hydrazine in alcohol chloroquinazoline gave 4-*quinazolylhydrazine* (X); unlike true hydrazines, this did not reduce copper salts in acetic acid, but was oxidised by Fehling's solution to quinazoline. These methods constitute two new syntheses of quinazoline, since dihydroquinazoline can be oxidised to quinazoline with ferricyanide (Gabriel, *Ber.*, 1903, **36**, 808). The latter method appeared more promising in view of the known sensitivity of 8-amino-6-methoxyquinoline to oxidation; (VII; R = Cl) was therefore converted by means of hydrazine in alcohol into 8-*nitro*-6-*methoxy*-4-*quinazolylhydrazine* (VII; R = $NH\cdot NH_2$) which, however, resisted oxidation by Fehling's solution or ferricyanide. With toluenesulphonyl chloride the *toluenesulphonyl* derivative was obtained, and by heating this with potassium carbonate in water (cf. McFadyen and Stevens, J., 1936, 584), a little 8-*nitro*-6-*methoxyquinazoline* (VII; R = H) was obtained; unfortunately, all attempts to raise the yield failed. It is likely that 4-quinazolylhydrazines react mainly in the tautomeric hydrazone form and therefore show abnormal reactions.


(X.)


(XI.)


(XII.)


(XIII.)

At this point circumstances required this line of work to be abandoned, but two other routes to (VII; R = H) have been explored. The condensation of **3 : 5-dinitro-2-methoxybenzaldehyde** with benzamidine gave **6 : 8-*dinitro*-2-*phenylquinazoline*** (XI), but this new quinazoline synthesis, based on Hill and Robinson's dinitrostrychol synthesis (J., 1933, 487), failed with acetamidine. An attempt was also made to condense 2-nitroacetanisidide with urethane in presence of phosphoric anhydride, following Sen and Rây (J., 1926, 646), but the only product isolated appeared to be ***5-methoxybenzfurazan*** (XII). Its volatility and analysis indicated the simple formula $C_7H_6O_2N_2$, including one methoxyl; it was neutral and stable to acids and alkalis, and in general had the properties expected for such a structure.

Finally, attempts were made to prepare quinazoline analogues of sulphadiazine, which is known to have antimalarial action. 4-Chloroquinazoline reacted easily with ammonia in alcohol to give ***4-aminoquinazoline*** (XIII; R = H, R′ = NH_2), but this very sparingly soluble substance was almost non-basic and was unchanged by acid halides even in boiling pyridine; probably it exists as an iminodihydroquinazoline, because the properties of the 4-quinazolylhydrazines and the ready reduction of the quinazoline ring suggest a peculiar stability of the 3 : 4-dihydro-form. Attempts were also made to condense acetylsulphanilamide or its sodium salt with 4-chloroquinazoline but under a variety of conditions none of the desired sulphonamide was obtained.

In contrast to 4-aminoquinazoline, the 2-*amino*-isomer (XIII; R = NH_2, R′ = H), prepared from 2-chloroquinazoline and ammonia, seemed quite normal in its properties and reacted readily with acetamidobenzenesulphonyl chloride and pyridine; unfortunately, the product was mostly alkali-insoluble, and probably nuclear acylation predominated. A small alkali-soluble fraction was obtained which appeared to be the required **2-(p-*acetamidobenzenesulphonamido*)*quinazoline*** (XIII; R = NHAc·C_6H_4·SO_2·NH, R′ = H), but the yield was extremely poor, and could not be improved.

Experimental.

(All salts were dried for analysis in a high vacuum at 60°.)

5 : 7-*Diphenyl*-4-*azahydrindene Methiodide* (as I; R, R′ = H).—A solution of diphenylazahydrindene (2 g.) (Stobbe and Volhard, *Ber.*, 1902, **35**, 3973) and methyl iodide (2 g.) in methanol (10 c.c.) was heated for 10 hours at 130° in a Carius tube. When cold, the *methiodide* was collected, and crystallised from water in superb golden needles with an adamantine lustre, m.p. 240° (decomp.) (Found: C, 60·8; H, 5·0; I, 30·8. $C_{21}H_{20}NI$ requires C, 61·0; H, 4·8; N, 30·8%).

5-*Phenyl*-7-(p-*anisyl*)-4-*azahydrindene Methiodide* (as I; R = H, R′ = OMe).—Prepared similarly, this *methiodide* was contaminated with much gummy water-insoluble material; it was purified by crystallisation from water, forming small, orange polyhedra, m. p. 250° (decomp.) (Found: C, 59·4; H, 4·9; I, 28·4. $C_{22}H_{22}ONI$ requires C, 59·6; H, 5·0; I, 28·6%).

5-*Phenyl*-7-(p-*dimethylaminophenyl*)-4-*azahydrindene* (I; R = H, R′ = NMe_2).—Prepared by the method of Stobbe and Volhard (*loc. cit.*) from *p*-dimethylaminobenzylideneacetophenone (13 g.), the base crystallised from alcohol in ochre bipyramids (8·2 g., 50%) containing a little recalcitrant impurity. The extremely deliquescent *hydrochloride* crystallised from ethyl acetate containing a little alcohol in orange prisms, m. p. 135° with gas-evolution (Found: C, 68·6; H, 6·7; N, 7·1. $C_{23}H_{22}N_2$,HCl,$2H_2O$ requires C, 68·3; H, 7·0; N, 7·2%). From the hydrochloride the pure *base* was regenerated, and crystallised from alcohol in long, flat, pale yellow, rhombic needles, m. p. 155° (Found: C, 84·0; H, 7·2; N, 8·8. $C_{23}H_{22}N_2$ requires C, 84·1; H, 7·0; N, 8·9%).

5-*Phenyl*-7-(m-*nitrophenyl*)-4-*azahydrindene* (II; R = NO_2, R′ = H).—Prepared similarly from *m*-nitrobenzylideneacetophenone (5 g.), the *azahydrindene* crystallised from aqueous alcohol in short, pale yellow prisms (5·1 g., 82%), m. p. 119—120° (Found: C, 74·4; H, 4·8; N, 8·8. $C_{20}H_{16}O_2N_2$,$\frac{1}{2}H_2O$ requires C, 74·5; H, 5·2; N, 8·7%).

5-*Phenyl*-7-(m-*aminophenyl*)-4-*azahydrindene*.—The nitro-compound (43·2 g.) was reduced in alcohol over Raney nickel with hydrogen at 100°/90 atm., and the *amine* distilled at 220—225°/0·1 mm. as a clear glass (23·1 g., 59%), which crystallised on fusion and slow cooling, m. p. 136—137° (Found: C, 83·6; H, 6·4; N, 9·8. $C_{20}H_{18}N_2$ requires C, 83·9; H, 6·3; N, 9·8%).

5-*Phenyl*-7-[m-(p-*acetamidobenzenesulphonamido*)*phenyl*]-4-*azahydrindene*.—*p*-Acetamidobenzenesulphonyl chloride (1·25 g.) was added to a solution of the amine (1·27 g.) in dry acetone (10 c.c.) and pyridine (0·7 c.c.). Next day, water was added, and the *acetylsulphonamide* collected; it crystallised from acetic acid in colourless, microscopic needles (1·45 g., 72%), m. p. 212° (decomp.) (Found, in material dried for 5 hours at 100°/20 mm.: C, 66·1; H, 5·3; N, 7·8. $C_{28}H_{25}O_3N_3S$,$C_2H_4O_2$ requires C, 66·3; H, 5·3; N, 7·7%).

5-*Phenyl*-7-[m-(p-*aminobenzenesulphonamido*)*phenyl*]-4-*azahydrindene*.—The crude acetylsulphonamide from the amine (3 g.) was dissolved in N-sodium hydroxide solution (100 c.c.) and boiled for 1 hour under reflux with charcoal (1 g.), filtered, and the *aminosulphonamide* precipitated with acetic acid and crystallised from aqueous alcohol, forming small colourless rhombohedra, m. p. 175° (Found, in material dried at 100°/20 mm.: C, 68·9; H, 5·2; S, 6·8. $C_{26}H_{23}O_3N_3S$,$\frac{1}{2}H_2O$ requires C, 68·9; H, 5·4; S, 7·1%). Diazotisation and coupling with β-naphthol gave an orange colour.

5-*Phenyl*-7-(p-*nitrophenyl*)-4-*azahydrindene*.—Prepared similarly from *p*-nitrobenzylideneacetophenone (46·8 g.), the *azahydrindene* crystallised from alcohol (charcoal) in colourless rosettes (54 g., 92%), m. p. 146—150°, raised by recrystallisation to 154—155° (Found: C, 74·5; H, 5·2; N, 8·4. $C_{20}H_{16}O_2N_2$,$\frac{1}{3}H_2O$ requires C, 74·5; H, 5·2; N, 8·7%. Found, in material dried at 100°/0·01 mm.: C, 74·8; H, 5·1. $C_{20}H_{16}O_2N_2$,$\frac{1}{4}H_2O$ requires C, 74·9; H, 5·1%).

5-*Phenyl*-7-(p-*aminophenyl*)-4-*azahydrindene*.—The nitro-compound (20 g.) was reduced as before to the *amine*, which distilled at 225—230°/0·1 mm. as a clear glass (14·1 g., 78%), and this crystallised from alcohol in long, pale yellow needles, m. p. 169° (Found, in material dried at 100°/20 mm.: C, 84·0; H, 6·4; N, 9·9. $C_{20}H_{18}N_2$ requires C, 83·9; H, 6·3; N, 9·8%).

5-*Phenyl*-7-[p-(p-*acetamidobenzenesulphonamido*)*phenyl*]-4-*azahydrindene*.—Prepared in the same way as its isomer, this *acetylsulphonamide* crystallised from 50% alcohol in pale yellow, hexagonal plates, m. p. 155° with sintering (Found: C, 67·8; H, 5·6; S, 5·8. $C_{28}H_{25}O_3N_3S$,C_2H_4O requires C, 68·1; H, 5·8; S, 6·0%).

5-*Phenyl*-7-[p-(p-*aminobenzenesulphonamido*)*phenyl*]-4-*azahydrindene*.—Prepared by alkali hydrolysis, the *aminosulphonamide* contained some of its sodium salt and was purified by solution in acetic acid and precipitation with ammonia; it then crystallised from aqueous alcohol in colourless rosettes, m. p. 132° (Found, in material dried at 100°/12 mm.: C, 68·3; H, 5·7; S, 7·0. $C_{26}H_{23}O_3N_3S$,H_2O requires C, 68·0; H, 5·4; S, 7·0%). The amorphous sodium salt was almost insoluble in water, and the azo-dye with β-naphthol was orange.

4-*Dimethylamino-4′-acetamidochalkone.*—Sodium hydroxide solution (20 c.c. of 20%) was added to *p*-acetamidoacetophenone (20·6 g.) and *p*-dimethylaminobenzaldehyde (17·5 g.) in alcohol (200 c.c.). Next day, water was added, and the *chalkone* collected; it crystallised from alcohol in orange prisms (16·5 g., 39%), m. p. 197—202°, raised by recrystallisation to 205° (Found: N, 9·3. $C_{19}H_{20}O_2N_2$ requires N, 9·1%).

4-*Acetamidophenacyl-4′-dimethylaminophenyl-2″-ketocyclopentylmethane.*—A mixture of the chalkone (9·6 g.), *cyclo*pentanone (6 g.), and piperidine (1 c.c.) was heated for 1 hour on a steam-bath. Crystallisation from alcohol (90%) gave bright yellow needles of the *diketone* (11·0 g., 90%), m. p. 125—128°, raised by recrystallisation to 130° (Found, in material dried at 100°/20 mm.: C, 71·6; H, 7·3; N, 7·2. $C_{24}H_{28}O_3N_2,\frac{1}{2}H_2O$ requires C, 71·8; H, 7·2; N, 7·0%).

5-(p-*Acetamidophenyl*)-7-(p-*dimethylaminophenyl*)-4-*azahydrindene.*—A mixture of the diketone (4·2 g.), hydroxylamine hydrochloride (5 g.), alcohol (70 c.c.), and hydrochloric acid (1 c.c., 35%) was boiled for 6 hours under reflux, and the base then precipitated with ammonia; since it gave a positive diazo-reaction, it was reacetylated with acetic anhydride on a steam-bath, and the resulting *azahydrindene* crystallised from aqueous alcohol in almost colourless needles, m. p. 123—124° with gas-evolution (Found, in material dried at 100°/0·01 mm.: C, 76·6; H, 6·8; N, 10·9. $C_{24}H_{25}ON_2,\frac{1}{4}H_2O$ requires C, 76·7; H, 6·8; N, 11·2%).

β-Diethylaminoethylaniline (III; R = H).—Powdered sodamide (2·3 g.) was added to a solution of aniline (6·3 g.) and *β*-chloroethyldiethylamine (9·15 g.) in toluene (25 c.c.), and the mixture heated in an oil-bath to 70° whereupon vigorous evolution of ammonia began. After ½ hour at 70° the bath temperature was raised during another ½ hour to 115°, and the solution then refluxed for 2½ hours. When it was cold, water was added, and the toluene layer separated and extracted with dilute acetic acid; from the acid layer the bases were isolated with alkali and ether and fractionated. *β*-Diethylaminoethylaniline was collected at 162—164°/25 mm. as a colourless liquid (8·4 g., 66%; 79% allowing for recovered aniline), $n_D^{20°}$ 1·5217 (Found: C, 74·7; H, 10·6. Calc. for $C_{12}H_{20}N_2$: C, 75·0; H, 10·4%). No crystalline derivative of this amine had been reported. The *monopicrolonate* crystallised from acetone in large rectangular orange tablets, m. p. 146—147° (Found: C, 58·2; H, 6·4; N, 17·4. $C_{12}H_{20}N_2,C_{10}H_8O_5N_4,\frac{1}{2}C_2H_6O$ requires C, 58·1; H, 6·4; N, 17·3%). The *dipicrolonate* crystallised from acetone containing picrolonic acid in lemon-yellow, pointed prisms, m. p. 160—162° (Found: C, 53·3; H, 5·3. $C_{12}H_{20}N_2,2C_{10}H_8O_5N_4$ requires C, 53·3; H, 5·0%). The *dipicrate* crystallised after 2 months from acetone and alcohol containing picric acid in short, orange prisms, m. p. 95—97° (Found: C, 44·3; H, 4·6. $C_{12}H_{20}N_2,2C_6H_3O_7N_3,\frac{1}{2}C_2H_6O$ requires C, 44·5; H, 4·3%). The monopicrolonate is the best derivative for characterisation.

β-Diethylaminoethylmethylaniline (III; R = Me).—Prepared similarly from methylaniline (35 g.), *β*-chloroethyldiethylamine (48·7 g.), sodamide (15·3 g.), and toluene (120 c.c.), the amine was collected at 165—170°/20 mm. as a colourless oil (56·4 g., 84%; 100% allowing for recovery), $n_D^{20°}$ 1·5243 (Found: C, 75·8; H, 10·7. Calc. for $C_{13}H_{22}N_2$: C, 75·7; H, 10·7%). No derivative had been reported; the *dipicrate* crystallised from alcohol–acetone containing picric acid in bright yellow, dendritic prisms, m. p. 153—155° (Found: C, 45·1; H, 4·7. $C_{13}H_{22}N_2,2C_6H_3O_7N_3,\frac{1}{2}C_2H_6O$ requires C, 45·3; H, 4·5%).

5-*Phenyl*-7-(m-*β-diethylaminoethylaminophenyl*)-4-*azahydrindene.*—Prepared in the same way as above from the amine (14·3 g.), chloroethyldiethylamine (7·5 g.), sodamide (2·2 g.), and toluene (30 c.c.), this base was converted into its *oxalate*, which crystallised from alcohol in bright yellow rhombs (15·7 g., 74%), m. p. 98—100° with gas-evolution (Found: C, 62·4; H, 6·5; N, 7·7. $C_{26}H_{31}N_3,2C_2H_2O_4,\frac{1}{2}H_2O$ requires C, 62·7; H, 6·3; N, 7·3%). The *hydrochloride*, prepared in ether, was a deliquescent, cream-coloured powder (Found: C, 63·1; H, 7·4; N, 8·7. $C_{26}H_{31}N_3,2HCl,2H_2O$ requires C, 63·2; H, 7·5; N, 8·5%). Recrystallisation was effected with difficulty by gradual addition of ether to a solution in acetone and alcohol, almost colourless needles, m. p. 138—140°, of a *monohydrate* separating (Found: C, 65·5; H, 7·2. $C_{26}H_{31}N_3,2HCl,H_2O$ requires C, 65·5; H, 7·3%).

5-*Phenyl*-7-(p-*β-diethylaminoethylaminophenyl*)-4-*azahydrindene.*—Prepared in the same way from the amine (6·45 g.), chloroethyldiethylamine (3·38 g.), sodamide (0·99 g.), and toluene (30 c.c.), the azahydrindene derivative was converted into its *oxalate*, which crystallised from alcohol in deliquescent, saffron-coloured needles (8·25 g., 86%), m. p. 141—142° with gas-evolution (Found: C, 61·4; H, 6·3; N, 7·3. $C_{26}H_{31}N_3,2C_2H_2O_4,H_2O$ requires C, 61·7; H, 6·3; N, 7·2%). The *hydrochloride*, prepared in ether, was an extremely deliquescent, orange powder, m. p. 75° with gas-evolution (Found: C, 64·7; H, 8·2; N, 7·4. $C_{26}H_{31}N_3,2HCl,2\frac{1}{2}C_2H_6O$ requires C, 64·9; H, 8·4; N, 7·3%).

9-*β-Diethylaminoethylharmine* (IV).—A mixture of powdered harmine (12 g.), chloroethyldiethylamine (9·5 g.), powdered sodamide (3 g.), and toluene (30 c.c.) was boiled for 3 hours under reflux, and the *base* isolated in the usual way, dissolved in light petroleum and filtered from some unchanged harmine, and then distilled; it (5·75 g., 33%) was collected at 205°/0·15 mm. as a viscous yellow syrup, $n_D^{22°}$ 1·5902 (Found: C, 73·7; H, 8·0; N, 13·1. $C_{19}H_{25}ON_3$ requires C, 73·3; H, 8·0; N, 13·5%). The *hydrochloride*, solutions of which had a superb blue-violet fluorescence, crystallised from 90% alcohol in colourless needles, m. p. 275° (decomp.) (Found: C, 56·9; H, 7·3; N, 10·8. $C_{19}H_{25}ON_3,2HCl,H_2O$ requires C, 56·7; H, 7·2; N, 10·5%).

Harmine Methobromide.—When methyl*iso*harmine and *γ*-phenoxypropyl bromide were heated together in alcohol under pressure, the only product was *harmine methobromide*, which crystallised from aqueous alcohol in colourless needles, m. p. 280° (decomp.) (Found: C, 54·8; H, 5·0; N, 9·2; Br, 26·6. $C_{14}H_{15}ON_2Br$ requires C, 54·7; H, 4·9; N, 9·1; Br, 26·0%).

3-*Nitro*-2-*acetamido*-5-*methoxytoluene.*—To a solution of acetic acid (80 c.c.) in nitric acid (140 c.c., *d* 1·5), stirred mechanically and kept below 0°, was added in portions 2-acetamido-5-methoxytoluene (67 g.). After 3 hours the solution was poured on ice, and the *nitro*-compound collected; it crystallised from alcohol in very pale yellow needles (60 g., 70%), m. p. 173—176°, raised by repeated recrystallisation from alcohol and then ethyl acetate to 187° (Found: C, 53·5; H, 5·5; N, 12·5. $C_{10}H_{12}O_4N_2$ requires C, 53·6; H, 5·3; N, 12·5%).

3-*Nitro*-5-*methoxy*-o-*toluidine.*—Hydrolysis of the acetyl derivative with hydrochloric acid gave the free *amine*, which crystallised from ethyl acetate in large, ruby prisms, m. p. 134° (Found: C, 53·0; H, 5·6; N, 15·4. $C_8H_{10}O_3N_2$ requires C, 52·7; H, 5·5; N, 15·4%).

12-*Methoxy*-10-*methylphenanthrazine* (IX).—Prepared by reduction of the nitromethoxytoluidine with zinc dust and alcoholic hydrochloric acid, followed by condensation with phenanthraquinone, the *phenanthrazine* crystallised from acetic acid in silvery fawn plates, m. p. 217—218° (Found: C, 80·2; H, 5·4. Found, in material dried at 120°/0·01 mm.: C, 80·3; H, 4·9. $C_{22}H_{16}ON_2,\frac{1}{2}C_2H_4O_2$ requires C, 80·0; H, 5·2%). The compound gave a violet coloration with sulphuric acid, and its yellow solution in benzene had a faint violet fluorescence.

3-*Nitro*-N-*acetyl*-5-*methoxyanthranilic Acid.*—To a suspension of powdered nitroacetamidomethoxytoluene (44 g.) in a solution of magnesium sulphate (60·3 g. of heptahydrate) in water (3 l.), stirred mechanically at 75—80°, was added powdered potassium permanganate (85·5 g.). After 3 hours, the *acetylanthranilic acid* (39·0 g.) was isolated in the usual way; it crystallised from acetic acid in small, chrome-yellow needles, m. p. 250° (decomp.) (Found: C, 47·3; H, 4·0; Ac, 17·5. $C_{10}H_{10}O_6N_2$ requires C, 47·2; H, 3·9; Ac, 16·9%).

3-*Nitro*-5-*methoxyanthranilic Acid.*—The acetyl derivative (8·2 g.) was heated for 5 hours on a steam-bath with hydrochloric acid (40 c.c. of 25%). On cooling, a yellow hydrochloride separated, which was collected and decomposed by crystallisation from water (500 c.c.) to give red-black prisms (6·02 g., 88%) of the free *anthranilic acid*; at 185° this was

converted into a red form with partial fusion and resolidification, and then melted at 225—226° (rapid heating) to a red liquid (Found: C, 45·4; H, 3·9; N, 13·2. $C_9H_8O_5N_2$ requires C, 45·3; H, 3·8; N, 13·2%).

8-Nitro-6-methoxy-4-quinazolone.—Prepared by heating a mixture of the anthranilic acid (11·5 g.) and formamide (11·5 g.) for 3 hours at 165°, the *quinazolone* crystallised from aqueous pyridine in pale yellow needles (10·9 g., 91%), m. p. 270° (decomp.) (Found: C, 49·1; H, 3·4; N, 18·7. $C_9H_7O_4N_3$ requires C, 48·9; H, 3·2; N, 19·0%).

4-Chloro-8-nitro-6-methoxyquinazoline (VII; R = Cl).—After a mixture of the quinazolone (5·7 g.), phosphorus pentachloride (10 g.), and phosphorus oxychloride (60 c.c.) had been boiled under reflux till solution was complete, and then evaporated to dryness under reduced pressure, the residue was extracted in a Soxhlet with light petroleum (b. p. 60—80°) to give orange rhombs of the *chloro*-compound (4·65 g., 75%), m. p. 144—147°, raised by recrystallisation to 149° (Found: N, 17·5; Cl, 14·9. $C_9H_6O_3N_3Cl$ requires N, 17·5; Cl, 14·8%).

8-Nitro-6-methoxy-4-quinazolylhydrazine (VII; R = NH·NH_2).—The chloro-compound (3·55 g.) was added to a solution of hydrazine hydrate (12 g.) in alcohol (50 c.c.), and after 1½ hours the *hydrazine* (2·86 g., 87%) was collected; it crystallised from butanol in orange-brown, microscopic needles, m. p. 202° (decomp.) (Found: C, 45·9; H, 4·0; N, 29·8. $C_9H_9O_3N_5$ requires C, 45·9; H, 3·8; N, 29·8%). Attempts to oxidise the hydrazine with copper salts or ferricyanide gave no new compound.

8-Nitro-6-methoxy-4-quinazolyl-p-toluenesulphonylhydrazine.—Prepared in pyridine from the hydrazine (2·13 g.), the *toluenesulphonyl* derivative was insoluble in all solvents except formic acid, from which it was precipitated by addition of water in microscopic, orange needles (3·32 g., 94%), m. p. 225° (decomp.) (Found: C, 49·3; H, 4·0; N, 18·3; S, 7·7. $C_{16}H_{15}O_5N_5S$ requires C, 49·3; H, 3·9; N, 18·0; S, 8·2%).

8-Nitro-6-methoxyquinazoline (VII; R = H).—A mixture of the toluenesulphonyl derivative (500 mg.), potassium carbonate (500 mg.), and water (5 c.c.) was boiled for 30 minutes under reflux. When cold, the solid was collected and extracted with boiling water (10 c.c.), from which, after charcoal treatment, the *quinazoline* separated on cooling as a brown powder (22 mg.), m. p. 168—170°. Recrystallisation gave saffron-coloured needles, m. p. 170° (Found: C, 51·1; H, 3·8; N, 19·6. $C_9H_7O_3N_3$,½H_2O requires C, 51·2; H, 3·7; N, 19·9%). The yield could not be improved.

Attempts to reduce 4-Chloroquinazoline.—Reduction in boiling xylene over palladised charcoal gave almost quantitatively dihydroquinazoline, characterised as its picrate, feathery, saffron-coloured needles from alcohol, m. p. 220—222° (lit. 215°) (Found: C, 46·2; H, 3·1; N, 19·5. Calc. for $C_8H_8N_2$,$C_6H_3O_7N_3$: C, 46·5; H, 3·0; N, 19·4%). Chemical reducing agents or the use of hydroxylic solvents led only to 4-substituted quinazolines. *4-Ethoxyquinazoline picrate* crystallised from toluene in long, yellow needles, m. p. 178° (Found: C, 47·7; H, 3·2. $C_{10}H_{10}ON_2$,$C_6H_3O_7N_3$ requires C, 47·6; H, 3·2%).

4-Quinazolylhydrazine (X).—Prepared from the chloroquinazoline and hydrazine hydrate in alcohol, the *hydrazine* crystallised from pyridine in pale yellow needles, m. p. 186° (decomp.) (rapid heating) (Found: C, 59·7; H, 4·6. $C_8H_8N_4$ requires C, 60·0; H, 5·0%). The compound did not reduce acid or neutral copper solutions, but with Fehling's solution or ferricyanide some quinazoline was produced, isolated as its picrate, long, saffron-coloured prisms from water, m. p. 185—186° (lit. 188—190°) (Found, in material dried at 80°/0·01 mm.: C, 44·3; H, 2·9; N, 18·7. Calc. for $C_8H_8N_2$,$C_6H_3O_7N_3$,H_2O: C, 44·6; H, 2·9; N, 18·6%).

6: 8-Dinitro-2-phenylquinazoline.—To a solution of benzamidine in chloroform, prepared from the hydrochloride (7 g.) and dried over potash, was added 3: 5-dinitro-2-methoxybenzaldehyde (6 g.) (Hill and Robinson, J., 1933, 487), and the whole was boiled for 4 hours under reflux. After evaporation to dryness and extraction with hot alcohol (500 c.c.), the residue crystallised from amyl alcohol in pale yellow needles of the *quinazoline*, m. p. 231—233° (Found: C, 57·0; H, 3·0; N, 18·8; OMe, 0·0. $C_{14}H_8O_4N_4$ requires C, 56·7; H, 2·7; N, 18·9%). The reaction failed with acetamidine.

5-Methoxybenzfurazan (XII).—To a solution of 2-nitro-4-methoxyacetanilide (12 g.) and urethane (8 g.) in xylene (30 c.c.) boiling gently under reflux, phosphoric oxide (35 g.) was gradually added, and boiling continued for a further 2 hours. When the mixture was cold, water and excess of sodium hydroxide were added, and the contents of the flask steam-distilled. After the xylene had been rejected, a yellow solid collected, which crystallised from light petroleum in beautiful, colourless needles, m. p. 97—98°, with the characteristic smell of benzfurazan, apparently *5-methoxybenzfurazan* (Found: C, 56·1, 56·0; H, 4·0, 3·9; N, 18·5, 18·4; OMe, 20·2. $C_7H_6O_2N_2$ requires C, 56·0; H, 4·0; N, 18·7; OMe, 20·7%). The compound was slightly soluble in boiling water, crystallising on cooling, very soluble in organic solvents except light petroleum and unaffected by boiling acid or alkali.

4-Aminoquinazoline.—4-Chloroquinazoline (4 g.) was dissolved in alcohol saturated with ammonia at 0° (20 c.c.), and the solution heated for 3 hours at 100° in a sealed tube. When cold, the solid separating was washed with dilute alkali and crystallised from pyridine, giving colourless plates of the *aminoquinazoline* (3 g., 85%), m. p. 259—260° (Found: C, 66·2; H, 4·7. $C_8H_7N_3$ requires C, 66·2; H, 4·8%). The compound was practically non-basic and under a variety of conditions failed to react with acid chlorides.

2-Aminoquinazoline.—Crude 2-chloroquinazoline (9 g.) was heated for 3 hours at 160° in an autoclave with alcoholic ammonia (75 c.c.), then evaporated to dryness, and the residue washed with dilute alkali. The residue was sublimed at 220°/20 mm., and then crystallised from alcohol to give arborescent, citron prisms of *2-aminoquinazoline* (4·3 g.), m. p. 198° (Found: C, 66·3; H, 5·1. $C_8H_7N_3$ requires C, 66·2; H, 4·8%). The same compound was formed in poor yield by heating *o*-aminobenzaldehyde with guanidine carbonate or cyanamide, or with methyl*iso*thiourea in amyl alcohol.

2-(p-Acetamidobenzenesulphonamido)quinazoline.—*p*-Acetamidobenzenesulphonyl chloride (0·40 g.) was added to a solution of the amine (0·24 g.) in dioxan (3 c.c.) and pyridine (0·2 g.) at 45°. Next day, water was added and a little *sulphonamide* extracted with alkali from the major non-acidic product; it was precipitated with acid and crystallised from alcohol in microscopic, colourless needles, m. p. 270° (Found, in material dried at 100°/0·01 mm.: N, 16·5. $C_{16}H_{14}O_3N_4S$ requires N, 16·4%).

4-Methoxyazobenzene-3-carboxylic Acid.—The hydroxy-acid was methylated with a large excess of methyl sulphate and sodium methoxide in methanol, and the resulting ester hydrolysed to the *methoxy-acid*, which crystallised from alcohol in bright orange needles, m. p. 142—144° (Found: C, 65·6; H, 4·9; N, 10·9. $C_{14}H_{12}O_3N_2$ requires C, 65·6; H, 4·7; N, 10·9%).

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DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received August 5th*, 1944.]

169. *Studies in the Indole Series. Part I. Attempted Preparation of Tryptophan from Tricyclic Compounds.*

By J. Elks, D. F. Elliott, and B. A. Hems.

Attempts to synthesise tryptophan from derivatives of 1-keto-2 : 3-dihydropentindole are described. A 2-carbalkoxy-derivative could not be prepared either by Dieckmann cyclisation of ethyl β-2-carbethoxyindole-3-propionate or by elimination of carbon monoxide from ethyl or *iso*amyl 1-keto-2 : 3-dihydropentindole-2-glyoxylate, although the analogous 1-keto-2-carbethoxy-1 : 2 : 3 : 4-tetrahydrocarbazole was prepared easily from the corresponding 2-glyoxylic ester.

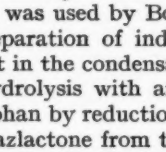
Bromination of 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole in neutral medium gave the same 6-bromo-derivative as bromination in acid medium.

Interest in the biological properties of individual amino-acids has led to the development of methods for their preparation in quantity. Most of them are readily accessible either by isolation from natural sources or by synthetic methods. Tryptophan is, however, an important exception; it is not abundantly present in any protein and its isolation from natural sources is troublesome. Until very recently four methods of synthesis had been reported, but none of these is convenient for preparing more than small quantities.

Ellinger and Flamand (*Z. physiol. Chem.*, 1908, **55**, 8; *Ber.*, 1907, **40**, 3029) synthesised tryptophan from indole-3-aldehyde by the azlactone method. Majima and Kotake (*Ber.*, 1922, **55**, 3859) prepared it from indolylidenehydantoin by reduction with sodium amalgam, followed by hydrolysis with baryta. A similar process was used by Boyd and Robson (*Biochem. J.*, 1935, **29**, 555, 2256), who developed a new method for the preparation of indolealdehyde, improved the yield of indolylidenehydantoin by using piperidine as a catalyst in the condensation, and converted the hydantoin into tryptophan in good yield by prolonged reductive hydrolysis with ammonium sulphide. Bauguess and Berg (*J. Biol. Chem.*, 1934, **104**, 679) prepared tryptophan by reduction of the oxime of indole-3-pyruvic acid, this acid being prepared by alkaline hydrolysis of the azlactone from the aldehyde (Ellinger and Matsuoka, *Z. physiol. Chem.*, 1920, **109**, 261).

After the completion of the work described in this and the following papers, another synthesis of tryptophan was described by Snyder and Smith (*J. Amer. Chem. Soc.*, 1944, **66**, 350) and Albertson, Archer, and Suter (*ibid.*, p. 500). Indole was condensed with formaldehyde and dimethylamine to give gramine, which was converted into the methiodide and thence, by condensation with ethyl acetamido- or benzamido-malonate, into ethyl acylamino(3-indolylmethyl)malonate. From this, tryptophan was prepared by hydrolysis to the malonic acid, decarboxylation and hydrolysis of the acyl group.

Attempts are reported in this and the following paper to find a new route to tryptophan which would avoid the troublesome preparation of indole and its 3-aldehyde. In this Part experiments involving the use of derivatives of 1-keto-2 : 3-dihydropentindole (I, R = H), and its homologue, 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole (II, R = H), are described.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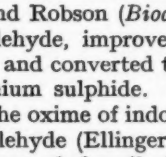
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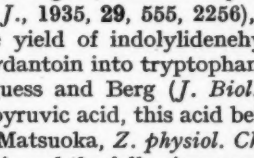
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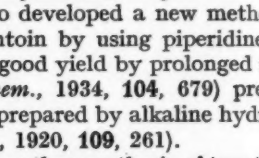

(IV.)

Our experiments were largely directed towards the preparation of 1-keto-2-carbethoxy-2 : 3-dihydropentindole, which might give rise, either by the action of hydrazoic acid (cf. Adamson, J., 1939, 1564) or by Beckmann rearrangment of its oxime, to the compound (III); from this, tryptophan should be obtainable by ring opening to (IV) and decarboxylation.

In the first series of experiments, attempts were made, under a variety of conditions, to prepare 1-keto-2-carbethoxy-2 : 3-dihydropentindole by Dieckmann cyclisation of ethyl β-2-carbethoxyindole-3-propionate (Kalb, Schweizer, and Schimpf, *Ber.*, 1926, **59**, 1858; Manske and Robinson, J., 1927, 240), but these were uniformly unsuccessful, much of the starting material being always recovered. Similar attempts to cyclise ethyl γ-2-carbethoxyindole-3-butyrate (Jackson and Manske, *J. Amer. Chem. Soc.*, 1930, **52**, 5029) also failed. Recently, Koelsch (*J. Org. Chem.*, 1943, **8**, 295) described a similar failure in attempts to cyclise ethyl β-2 : 6-dicarbethoxyindole-3-propionate.

Attention was next turned to the possibility of converting 1-keto-2 : 3-dihydropentindole (I, R = H) into the 2-carbethoxy-compound. Lions (*Proc. Roy. Soc. N.S.W.*, 1933, **66**, 516) prepared *cyclo*pentane-1 : 2-dione monophenylhydrazone by reaction between benzenediazonium chloride and ethyl *cyclo*pentanone-2-carboxylate (see also Dieckmann, *Annalen*, 1901, **317**, 63; Linstead and Wang, J., 1937, 807), and Manske (*Canadian J. Res.*, 1931, **4**, 595) has cyclised this compound to 1-keto-2 : 3-dihydropentindole by treatment with aqueous-alcoholic hydrogen chloride. We prepared the phenylhydrazone by the action of benzenediazonium chloride upon 2-formyl*cyclo*pentanone, and cyclised it by boiling with dilute sulphuric acid. The ketone differs considerably from 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole (Coffey, *Rec. Trav. chim.*, 1923, **42**, 528; Kent, J., 1935, 976; Lions, *loc. cit.*), having a much higher melting point and being much less soluble in the usual solvents.

These two keto-compounds reacted with ethyl oxalate in cold alcoholic sodium ethoxide to give *ethyl 1-keto-2 : 3-dihydropentindole-2-glyoxylate* (I, R = $CO{\cdot}CO_2Et$) and *ethyl 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole-2 glyoxylate* (II, R = $CO{\cdot}CO_2Et$), respectively. On heating, the latter lost carbon monoxide to give 1-*keto*-2-

carbethoxy-1 : 2 : 3 : 4-*tetrahydrocarbazole*, but the former could not be converted into the carbethoxy-compound, though many attempts were made to carry out the reaction, both at ordinary pressure and in a vacuum, and in presence and absence of catalysts. Since the high melting point of the glyoxylic ethyl ester may have been responsible for the failure to effect removal of carbon monoxide, the corresponding iso*amyl* ester (I, R = $CO{\cdot}CO_2C_5H_{11}$) was prepared in a similar manner in the hope that it might have a sufficiently low melting point to lose carbon monoxide on fusion, without undergoing extensive decomposition. The ester did, in fact, have a considerably lower melting point than the ethyl ester but, again, it was not possible to obtain the carboxylic acid ester from it.

The direct introduction of a carbethoxy-group into 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole by means of ethyl carbonate (Wallingford, Homeyer, and Jones, *J. Amer. Chem. Soc.*, 1941, **63**, 2252), and of a formyl group by means of ethyl formate, was not achieved.

Attempts to oxidise 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole to the 1 : 2-diketone *via* the *iso*nitroso-compound, or directly by means of selenium dioxide in alcohol, benzene, or acetic acid, also met with no success.

Bromination of 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole in acetic acid has been shown by Mears, Oakeshott, and Plant (J., 1934, 272) to lead to the 6-bromo-compound. We have found that the same compound is obtained when the reaction is maintained neutral by bromination in chloroform solution in the presence of calcium carbonate.

Experimental.

cyclo*Pentane*-1 : 2-*dione Monophenylhydrazone*.—A mixture of *cyclo*pentanone (21 g.) and ethyl formate (18·5 g.) was cooled to − 20° and added to a solution of sodium ethoxide, prepared from sodium (6 g.) and anhydrous ethyl alcohol (85 c.c.), also at − 20°. The mixture was kept at − 20° for 30 minutes and then at 0° overnight. Ice-water was added to dissolve the solid sodium salt of 2-hydroxymethylene*cyclo*pentanone, and the solution neutralised to Congo-red by addition of dilute acetic acid at 0°. This solution was added gradually, with stirring, to a solution of benzenediazonium hydroxide, prepared by diazotising aniline (18·5 g.) in 5N-hydrochloric acid (95 c.c.) with sodium nitrite (16 g. in 40 c.c. of water), neutralising it at 0°, and filtering. The resulting orange precipitate was filtered off after 2 hours (longer standing gave a darker product in smaller yield), washed with water, and recrystallised from ethyl alcohol. *cyclo*Pentane-1 : 2-dione monophenylhydrazone separated in orange-brown needles, m. p. 199—200° (Lions, *loc. cit.*, gives m. p. 203°) (yield 22 g.; 59%).

1-*Keto*-2 : 3-*dihydropentindole* (I, R = H).—The foregoing phenylhydrazone (6·3 g.) was boiled for a few minutes with a solution of concentrated sulphuric acid (7 c.c.) in water (70 c.c.), and the mixture then digested on the water-bath for 1 hour. The cooled mixture was filtered, and the residue crystallised from ethyl alcohol after treatment with charcoal. 1-Keto-2 : 3-dihydropentindole separated as yellowish leaflets (2·9 g.; 51%), m. p. 249—251° (decomp.) (Found: C, 77·0; H, 5·3; N, 8·2. Calc. for $C_{11}H_9ON$: C, 77·2; H, 5·3; N, 8·2%). Manske, *loc. cit.*, gives m. p. 248—249°.

On a larger scale it was necessary to boil the mixture for 1½ hours in order to ensure complete reaction. Owing to the sparing solubility of the product in ethyl alcohol, larger quantities were best purified by dissolving it in chloroform, adding a large quantity of alcohol, and distilling off the chloroform till crystallisation began. The overall yield of 1-keto-2 : 3-dihydropentindole from aniline could be increased to 40% by omitting the crystallisation of the phenylhydrazone.

Ethyl 1-*Keto*-2 : 3-*dihydropentindole*-2-*glyoxylate* (I, R = $CO{\cdot}CO_2Et$).—A mixture of 1-keto-2 : 3-dihydropentindole (20 g.) and ethyl oxalate (18 g.) was treated at 0° with a solution of sodium ethoxide, prepared from sodium (3·0 g.) and anhydrous alcohol (60 c.c.). The mixture was left at 0° for 2 days, and then acidified with dilute sulphuric acid. The orange-yellow solid was filtered off, and crystallised from ethyl alcohol or glacial acetic acid, *ethyl* 1-*keto*-2 : 3-*dihydropentindole*-2-*glyoxylate* being obtained as yellow crystals, m. p. 222—223° (decomp.) (Found: C, 66·4; H, 4·8; N, 5·6. $C_{15}H_{13}O_4N$ requires C, 66·4; H, 4·8; N, 5·2%); yield 24 g., 76%.

iso*Amyl* 1-*Keto*-2 : 3-*dihydropentindole*-2-*glyoxylate* (I, R = $CO{\cdot}CO_2C_5H_{11}$).—*iso*Amyl oxalate was prepared in 92% yield by refluxing a mixture of oxalic acid (143 g.), *iso*amyl alcohol (220 g.), and carbon tetrachloride (200 c.c.) in a flask fitted with a device which retained the water distilling out with carbon tetrachloride. The ester boiled at 144°/14 mm. Sodium (1·3 g.) was dissolved in boiling *iso*amyl alcohol (30 c.c.), the solution added to a mixture of 1-keto-2 : 3-dihydropentindole (8·6 g.) and *iso*amyl oxalate (12 g.), and the mixture heated on the water-bath for 4 hours. Water and excess of sulphuric acid were added to the cooled mixture, followed by ethyl alcohol to facilitate filtration. The yellow solid was crystallised from glacial acetic acid, giving iso*amyl* 1-*keto*-2 : 3-*dihydropentindole*-2-*glyoxylate*, m. p. 184—185° (decomp.) (Found: C, 68·6; H, 6·3; N, 4·6. $C_{18}H_{19}O_4N$ requires C, 69·0; H, 6·1; N, 4·5%); yield 9·5 g., 60%.

Ethyl 1-*Keto*-1 : 2 : 3 : 4-*tetrahydrocarbazole*-2-*glyoxylate* (II, R = $CO{\cdot}CO_2Et$).—A mixture of 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole (20 g.) and ethyl oxalate (16 g.) was treated at 0° with a solution of sodium ethoxide from sodium (2·5 g.) and anhydrous alcohol (50 c.c.), and the product worked up and crystallised as for (I, R = $CO{\cdot}CO_2Et$). *Ethyl* 1-*keto*-1 : 2 : 3 : 4-*tetrahydrocarbazole*-2-*glyoxalate* was obtained as yellow crystals, m. p. 155—156° (Found: C, 67·9; H, 5·55; N, 5·3. $C_{16}H_{15}O_4N$ requires C, 67·35; H, 5·3; N, 4·9%); yield 23 g., 75%. A solution of the compound in alcohol gave an intense brown colour on addition of ferric chloride.

Ethyl 1-*Keto*-1 : 2 : 3 : 4-*tetrahydrocarbazole*-2-*carboxylate*.—The preceding ester (20 g.) was heated under reflux at 200—220°. When gas-evolution slackened, the bath temperature was raised to 240° and maintained thereat till no more gas was evolved. The resulting reddish oil solidified on cooling, and after crystallisation from ethyl alcohol (charcoal), gave *ethyl* 1-*keto*-1 : 2 : 3 : 4-*tetrahydrocarbazole*-2-*carboxylate* as colourless needles, m. p. 145—146° (Found: C, 69·6; H, 6·2; N, 5·5. $C_{15}H_{15}O_3N$ requires C, 70·0; H, 5·9; N, 5·45%); yield 10·8 g., 60%. A solution of this compound in ethyl alcohol gave a green colour on addition of ferric chloride.

6-*Bromo*-1-*keto*-1 : 2 : 3 : 4-*tetrahydrocarbazole*.—Bromine (2 c.c.) was added slowly to a vigorously stirred mixture of 1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole (5 g.) in chloroform (60 c.c.) and calcium carbonate (4 g.), and stirring was thereafter continued for 1½ hours. Hydrochloric acid was added, and the residual solid was filtered off and crystallised from alcohol, 6-bromo-1-keto-1 : 2 : 3 : 4-tetrahydrocarbazole being obtained, m. p. 220—221°, undepressed on admixture with a specimen prepared by the method of Mears, Oakeshott, and Plant (*loc. cit.*), who give m. p. 222—224°. A further quantity of the compound was obtained by separating the chloroform layer, drying it over calcium chloride, and evaporating it to dryness.

The authors wish to thank Miss V. M. Witherow for assistance in some of the experimental work.

Glaxo Laboratories Ltd., Greenford, Middlesex. [*Received, August 16th*, 1944.]

170. *Studies in the Indole Series. Part II. Attempted Synthesis of Tryptophan from Substituted Malonic Esters.*

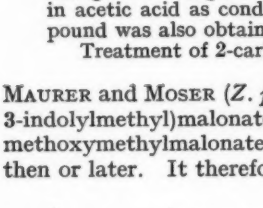
By J. Elks, D. F. Elliott, and B. A. Hems.

Some attempts to synthesise tryptophan from ethyl (2-carbethoxy-3-indolylmethyl)malonate and related compounds are described. Attempts to halogenate this ester in the α-position were unsuccessful; on bromination, substitution in the 5-position occurred, but sulphuryl chloride was without effect.

Bromination of ethyl methoxymethylmalonate led to ethyl αβ-dibromomethylmalonate, which reacted with potassium phthalimide to give ethyl α-bromo-β-phthalimidomethylmalonate. Condensation of ethyl α-phthalimido-β-methoxymethylmalonate, for which an improved synthesis is described, with 2-carbethoxyindole did not give the expected ethyl phthalimido(2-carbethoxy-3-indolylmethyl)malonate; with hydrogen bromide in acetic acid as condensing agent, ethyl α-phthalimido-β-acetoxymethylmalonate was obtained. This compound was also obtained from ethyl phthalimidomalonate and paraformaldehyde in acetic acid or anhydride.

Treatment of 2-carbethoxyskatole with sulphuryl chloride gave 1-hydroxy-2-carbethoxyskatole.

Maurer and Moser (*Z. physiol. Chem.*, 1926, **161**, 131) have described the preparation of ethyl (2-carbethoxy-3-indolylmethyl)malonate (I; R = Et, R′ = R″ = H) by the condensation of 2-carbethoxyindole and ethyl methoxymethylmalonate. They claimed to have prepared tryptophan from it, but did not give details either then or later. It therefore appeared desirable to investigate their claims, and attempts to synthesise tryptophan from this ester and related compounds are now described.

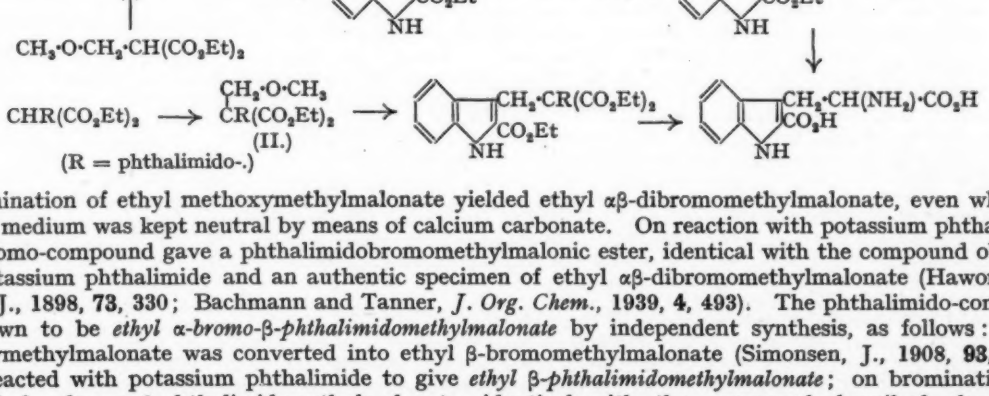


(I).

Some difficulties were encountered in the preparation of ethyl methoxymethylmalonate (Simonsen, J., 1908, **93**, 1780), an attempt to fractionate the product through a column at about 15 mm. pressure leading to its destruction and formation of a polymer of ethyl methylenemalonate. The mixture was separated by distillation through a column at a pressure of about 1 mm., but the yield was still less than that obtained by Simonsen. The use of benzene in place of ether in the reaction between sodiomalonic ester and chlorodimethyl ether, as described by Fischer and Nenitzescu (*Annalen*, 1925, **443**, 125), did not prove satisfactory in our hands and an attempt with magnesium replacing sodium (cf. Spassow, *Ber.*, 1937, **70**, 2381) failed completely.

All attempts to brominate (2-carboxy-3-indolylmethyl)malonic acid (I; R = R′ = R″ = H) (Maurer and Moser, *loc. cit.*) failed, probably because of the very low solubility of the acid in the usual solvents. Bromination of the corresponding triethyl ester gave a monobromo-compound which was not the expected ethyl bromo(2-carbethoxy-3-indolylmethyl)malonate (I; R = Et, R′ = Br, R″ = H); prolonged alkaline hydrolysis converted it into a tricarboxylic *acid* still containing bromine. The compound was shown to be *ethyl* (*5-bromo-2-carbethoxy-3-indolylmethyl*)*malonate* (I; R = Et, R′ = H, R″ = Br) by comparison with a specimen prepared from 5-bromo-2-carbethoxyindole (Hughes *et al.*, *Proc. Roy. Soc. N.S.W.*, 1938, **71**, 475) and ethyl methoxymethylmalonate. Treatment of (I; R = Et, R′ = Br, R″ = H) with sulphuryl chloride in an attempt to obtain ethyl chloro(2-carbethoxy-3-indolylmethyl)malonate (I; R = Et, R″ = H, R′ = Cl) gave unchanged starting material as the only identifiable product.

Since the above reactions seemed to render the intended route to tryptophan impracticable, attention was turned to the preparation of suitably substituted malonic esters, which might be condensed with indole-2-carboxylic ester to give derivatives of tryptophan. The following scheme indicates the methods envisaged:



Bromination of ethyl methoxymethylmalonate yielded ethyl αβ-dibromomethylmalonate, even when the reaction medium was kept neutral by means of calcium carbonate. On reaction with potassium phthalimide, the dibromo-compound gave a phthalimidobromomethylmalonic ester, identical with the compound obtained from potassium phthalimide and an authentic specimen of ethyl αβ-dibromomethylmalonate (Haworth and Perkin, J., 1898, **73**, 330; Bachmann and Tanner, *J. Org. Chem.*, 1939, **4**, 493). The phthalimido-compound was shown to be *ethyl α-bromo-β-phthalimidomethylmalonate* by independent synthesis, as follows: Ethyl methoxymethylmalonate was converted into ethyl β-bromomethylmalonate (Simonsen, J., 1908, **93**, 1783), which reacted with potassium phthalimide to give *ethyl β-phthalimidomethylmalonate*; on bromination this gave ethyl α-bromo-β-phthalimidomethylmalonate, identical with the compound described above. An attempt to replace the bromine atom by a methoxy-group was unsuccessful; treatment with sodium methoxide gave phthalimide itself.

The preparation of ethyl phthalimidomethoxymethylmalonate (II) by Mitra's method (*J. Indian Chem. Soc.*, 1930, **7**, 800) was unsatisfactory, but the compound was obtained conveniently and in good yield

by the action of monochlorodimethyl ether upon sodiophthalimidomalonic ester (Dunn and Smart, *J. Biol. Chem.*, 1930, **89**, 46) in boiling benzene (cf. Maeda, Turumi, and Suzuki, *Bull. Inst. Phys. Chem. Res., Tokyo*, 1940, **19**, 267, who prepared the compound from the same reagents but in the absence of a solvent). Many attempts were made to condense the ester (II) with indole-2-carboxylic ester, but the presence of the phthalimido-group makes the condensation much more difficult. Alcoholic or acetic acid solutions of hydrogen chloride or bromide did not effect condensation, nor did sodium in benzene or toluene. Reaction in methyl-alcoholic sodium methoxide solution gave, in addition to unchanged materials, a very small quantity of a substance which, from its analysis, was not the expected compound and has not been identified.

When a solution of hydrogen bromide in acetic acid was used in the reaction, a compound which could also be obtained by the action of the same acid mixture upon ethyl phthalimidomethoxymethylmalonate was isolated. The same compound was prepared by the action of paraformaldehyde on ethyl phthalimido-malonate in acetic acid or anhydride solution in presence of zinc chloride. Analysis indicated the presence of three terminal methyl groups, and on hydrolysis the compound gave acetic acid, isolated and identified as the *p*-phenylphenacyl ester. These properties, together with the analytical figures, show that the compound is *ethyl phthalimidoacetoxymethylmalonate*. In view of the above results, this approach to the synthesis of tryptophan was abandoned.

It seemed possible that compounds related to tryptophan might be obtainable from ethyl skatole-2-carboxylate by condensation with suitable reactants. Several methods of preparing this ethyl ester are on record (Kermack, Perkin, and Robinson, J., 1921, **119**, 1634; Giua, *Atti Congr. Naz. Chim. Ind.*, 1924, 266; Wislicenus and Arnold, *Ber.*, 1887, **20**, 3395; *Annalen*, 1888, **246**, 334), and we found the Fischer cyclisation of ethyl propionylformate phenylhydrazone (cf. Wislicenus and Arnold, *loc. cit.*) to be convenient. This compound was prepared by the action of benzenediazonium chloride on ethyl ethylacetoacetate (Japp and Klingemann, *Ber.*, 1887, **20**, 2943; *Annalen*, 1888, **247**, 216).

Ethyl skatole-2-carboxylate could not be oxidised to 2-carbethoxyindole-3-aldehyde by means of selenium dioxide in benzene or acetic acid, only compounds of high m. p. being obtained, nor could it be condensed with ethyl oxalate, *p*-nitrosodimethylaniline, or ethyl mesoxalate, although a variety of conditions were used.

When ethyl skatole-2-carboxylate was treated with sulphuryl chloride in acetic acid, and the reaction mixture poured into water, a substance was isolated, the analysis of which agrees with that of *1-hydroxy-2-carbethoxyskatole*. This formulation of the compound is supported by its solubility in alkali, in agreement with the properties of known *N*-hydroxy-indoles, and by the fact that two molecules of acetic acid are produced on oxidation with chromic acid, showing that the 3-methyl group has not been attacked.

Experimental.

Ethyl Methoxymethylmalonate.—Various modifications of Simonsen's method (*loc. cit.*) were used, of which the following gave the most satisfactory results. Sodium (11·5 g.) was powdered under toluene, the toluene decanted, and the sodium washed with ether by decantation. Dry ether (300 c.c.) was added, followed by ethyl malonate (80 g.). The mixture was stirred mechanically until all the sodium had reacted (2—3 hours). The flask was cooled in ice, and monochlorodimethyl ether (50 g.), dissolved in dry ether (50 c.c.), was added slowly with vigorous stirring, the mixture then being stirred for 2 hours at room temperature. Water was added, the ethereal layer separated, and the aqueous layer washed with ether. The combined ethereal extracts were washed with water and dried over calcium chloride; the ether was removed, and the residue distilled in a vacuum, a short fractionating column being used. Ethyl methoxymethylmalonate distilled at 79—83°/0·8 mm.; yield 40—45 g., 39—44%. The ester deteriorates on standing.

In another experiment on the same scale, the product was fractionally distilled at 15 mm. pressure. The liquid, b. p. 100—120°, partly polymerised to a white solid, which was filtered off after addition of petrol to the semi-solid mass. The solid (18 g.) melted at 153—154° after crystallisation from ethyl alcohol [Found: C, 55·6; H, 7·0. Calc. for $(C_8H_{12}O_4)_n$: C, 55·8; H, 7·0%]. Haworth and Perkin (*loc. cit.*) describe a polymer of ethyl methylenemalonate, m. p. 146—150°.

Ethyl (2-Carbethoxy-3-indolylmethyl)malonate.—This compound was prepared from 2-carbethoxyindole and freshly distilled ethyl methoxymethylmalonate as described by Maurer and Moser (*loc. cit.*), but their yield of 90% could not be obtained, our maximum being 60%.

Ethyl (5-Bromo-2-carbethoxy-3-indolylmethyl)malonate.—(a) *By bromination of ethyl (2-carbethoxy-3-indolylmethyl)-malonate.* Bromine (1 g.), dissolved in chloroform (10 c.c.), was added gradually at room temperature to a solution of the ester (2 g.) in chloroform (20 c.c.). After 3 hours the chloroform was distilled off; the residual oil rapidly solidified, and melted at 159—160° after crystallisation from benzene–petrol (b. p. 60—80°) (Found: C, 51·8; H, 5·25; Br, 18·9. $C_{19}H_{22}O_6NBr$ requires C, 51·8; H, 5·0; Br, 18·2%); yield 1·9 g., 78%.

The *ester* (1 g.) was hydrolysed to the corresponding *acid* by refluxing for 2 hours with alcoholic sodium hydroxide (10%; 15 c.c.). The acid obtained by dilution with water, acidification, and ether extraction melted at 236—237° after crystallisation from acetone–petrol (b. p. 60—80°) (Found: C, 44·5; H, 3·9; N, 4·3. $C_{15}H_{14}O_6NBr$ requires C, 43·8; H, 2·8; N, 3·9%). The acid was converted into the *trimethyl* ester by refluxing for 6 hours with a 5% solution of hydrogen chloride in methyl alcohol. Crystals separated on standing overnight, and after recrystallisation from methyl alcohol had m. p. 179—180° (Found: C, 48·2; H, 3·9; Br, 20·3. $C_{16}H_{16}O_6NBr$ requires C, 48·3; H, 4·05; Br, 20·1%).

(b) *From 5-bromo-2-carbethoxyindole.* The method described by Hughes *et al.* (*loc. cit.*) for the preparation of 5-bromo-2-carbethoxyindole proved unsatisfactory, and the following modification was used. Ethyl pyruvate *p*-bromophenylhydrazone (20·4 g.), prepared as described by these authors, was added to a mixture of glacial acetic acid (75 c.c.) and concentrated sulphuric acid (5·4 c.c.). The mixture, after refluxing for 10 minutes, was poured into water (750 c.c.). The solid was filtered off and crystallised several times from ethyl alcohol (charcoal), giving 5-bromo-2-carbethoxyindole, m. p. 154—156° (Hughes *et al.* give m. p. 153°); yield 6·9 g., 36%. This compound (1·5 g.) was dissolved in ethyl alcohol (11 c.c.), ethyl methoxymethylmalonate (2 c.c.) and concentrated hydrochloric acid (2 c.c.) added, and the mixture refluxed for 2 hours. Dilution with water gave an oil which soon solidified. Crystallisation from benzene–petrol (b. p. 60—80°) gave a solid, m. p. 158—160°, not depressed on admixture with a specimen of the ester prepared

as in (a); yield 1·2 g., 49%. The corresponding acid and trimethyl ester were prepared, and shown by mixed m. p.'s to be identical with the corresponding derivatives described above.

Ethyl αβ-Dibromomethylmalonate.—(a) *From ethyl methoxymethylmalonate.* A solution of ethyl methoxymethylmalonate (20 g.) in carbon tetrachloride (20 c.c.) was warmed gently, and a solution of bromine (5·4 c.c.) in carbon tetrachloride (10 c.c.) added at such a rate that the solution boiled gently without external heating. The solution was then refluxed until it was almost colourless and no more hydrogen bromide was evolved. The cold solution was washed with 5% sodium carbonate solution, then with water, and dried over calcium chloride. The solvent was removed, and the residue distilled in a vacuum. Ethyl αβ-dibromomethylmalonate distilled at 124—126°/2 mm. A satisfactory analysis could not be obtained, the value for bromine always being considerably low, presumably owing to decomposition during distillation (Found: C, 34·3; H, 4·75; Br, 39·8; OEt, 30·1. Calc. for $C_8H_{12}O_4Br_2$: C, 28·9; H, 3·65; Br, 48·2; OEt, 27·2%). However, the analysis, together with the formation of ethyl α-bromo-β-phthalimidomethylmalonate on treatment with potassium phthalimide (see below), indicates that the product was mainly the dibromo-ester. A similar product was obtained when the reaction was carried out in presence of calcium carbonate (15 g.).

(b) *From ethyl methylenemalonate.* This ester was prepared from its polymer, described above (Haworth and Perkin, *loc. cit.*), or by Bachmann and Tanner's method (*loc. cit.*). A 20% solution of bromine in chloroform was added to an ice-cold solution of the ester (9·9 g.) in chloroform (50 c.c.) till a faint permanent colour remained in the solution. The chloroform was removed in a vacuum, leaving ethyl αβ-dibromomethylmalonate as a reddish oil (18 g.), which was used without further purification.

Ethyl Bromophthalimidomethylmalonate.—(a) *From ethyl αβ-dibromomethylmalonate.* This ester (3·3 g.) and potassium phthalimide (1·8 g.) were heated together at 150° for 2 hours, potassium bromide removed from the cooled product by trituration with water, and the residual solid filtered off and extracted with boiling ethyl alcohol. *Ethyl bromophthalimidomethylmalonate* formed white crystals, which, after further crystallisation from ethyl alcohol, melted at 137—138° (Found: C, 48·3; H, 3·9; N, 3·7; Br, 20·0; OEt, 21·9. $C_{16}H_{16}O_6NBr$ requires C, 48·2; H, 4·05; N, 3·5; Br, 20·1; OEt, 22·6%); yield 2·2 g., 55%.

(b) *Unambiguous synthesis.* Ethyl β-bromomethylmalonate (Simonsen, *loc. cit.*) (10 g.), potassium phthalimide (7·4 g.), and xylene (40 c.c.) were refluxed for 3 hours. After cooling, potassium bromide was filtered off, and xylene removed from the filtrate by distillation in a vacuum. The residual oil, which solidified slowly on standing, was crystallised from ether, giving *ethyl β-phthalimidomethylmalonate*, m. p. 91—92° (Found: C, 59·9; H, 5·9; N, 3·8. $C_{16}H_{17}O_6N$ requires C, 60·2; H, 5·4; N, 4·4%).

Uncrystallised phthalimido-ester, obtained as above from ethyl β-bromomethylmalonate (5 g.), was dissolved in chloroform (25 c.c.), and the solution refluxed while a solution of bromine (1·1 c.c.) in chloroform (5 c.c.) was added slowly, and then for a further hour. After distillation of the chloroform the residual oil soon solidified; after crystallisation from ethyl alcohol, ethyl α-bromo-β-phthalimidomethylmalonate was obtained as white crystals, m. p. 135—136°, not depressed on admixture with a specimen prepared as in (a); yield 2·7 g., 34% (based on ethyl β-bromomethylmalonate).

Ethyl Phthalimidomethoxymethylmalonate.—A suspension of finely powdered sodiophthalimidomalonic ester (Dunn and Smart, *loc. cit.*) (10 g.) in dry benzene (50 c.c.) was refluxed and stirred while a solution of monochlorodimethyl ether (5 g.) in benzene (10 c.c.) was added gradually. After a further hour's boiling, the solution was cooled, water added, the mixture filtered, and the benzene layer separated. The aqueous layer was washed with benzene, and the combined benzene solutions were washed with water and dried over sodium sulphate. The benzene was removed, and the residue of ethyl phthalimidomethoxymethylmalonate crystallised from ethyl alcohol, forming white crystals, m. p. 132—133° (Maeda, Turumi, and Suzuki, *loc. cit.*, give m. p. 133°); yield 7·8 g., 73%.

Ethyl Phthalimidoacetoxymethylmalonate.—(a) *From ethyl phthalimidomethoxymethylmalonate.* A mixture of the ester (2 g.) and hydrogen bromide in acetic acid (50%; 10 c.c.) was heated at 60° for 3 hours, and the clear solution cooled and poured into water. The resulting oil soon solidified and was crystallised from ethyl alcohol, giving *ethyl phthalimidoacetoxymethylmalonate* as colourless prisms, m. p. 110—111° (Found: C, 57·4; H, 5·0; N, 3·9; terminal CH_3, 14·9; *M*, 382. $C_{18}H_{19}O_8N$ requires C, 57·3; H, 5·1; N, 3·7; terminal CH_3, 12·0%; *M*, 377). The presence of an acetyl group in the molecule was established by hydrolysing the substance (0·98 g.) with boiling sulphuric acid (50%; 100 c.c.) for 1 hour. The solution was steam-distilled, the distillate neutralised with sodium hydroxide solution, evaporated in a vacuum to about 3 c.c., and boiled for 2 hours with *p*-phenylphenacyl bromide (0·65 g.) and ethyl alcohol (6 c.c.). The resulting solid, after crystallisation from ethyl alcohol, had m. p. 107—108° not depressed by authentic *p*-phenylphenacyl acetate (Found: C, 75·65; H, 5·7. Calc. for $C_{16}H_{14}O_3$: C, 75·6; H, 5·55%).

The same malonate was obtained when ethyl phthalimidomethoxymethylmalonate and 2-carbethoxyindole and hydrogen bromide in acetic acid were boiled under reflux.

(b) *From ethyl phthalimidomalonate.* Ethyl phthalimidomalonate (5 g.), paraformaldehyde (1 g.), fused zinc chloride (1 g.), and acetic anhydride (10 c.c.) were refluxed for 6 hours. The excess of acetic anhydride was destroyed by boiling for a short time with water. The resulting oil solidified on standing, and after crystallisation from ethyl alcohol gave ethyl phthalimidoacetoxymethylmalonate, m. p. 110—111°, undepressed on admixture with a sample prepared as in (a); yield 1·35 g., 22%.

The following variations were tried in an effort to increase the yield: (i) omission of zinc chloride gave only 0·9 g. of product; (ii) omission of zinc chloride and doubling the amount of paraformaldehyde gave 0·65 g. of product; (iii) replacement of acetic anhydride by acetic acid did not alter the yield; (iv) use of hydrogen chloride in acetic acid at room temperature gave only unchanged ethyl phthalimidomalonate.

Ethyl Propionylformate Phenylhydrazone.—Ethyl ethylacetoacetate (32 g.) was dissolved in a mixture of ethyl alcohol (150 c.c.) and aqueous sodium hydroxide (20%; 150 c.c.) previously cooled to − 10°. The solution was kept below − 5° and stirred while a solution of benzenediazonium chloride, prepared from aniline (19·5 g.), hydrochloric acid (4N; 166 c.c.), and sodium nitrite (14·2 g.), was added gradually. After addition was complete, the mixture was kept at − 5° for 30 minutes, acidified with dilute hydrochloric acid, and diluted with 1 l. of water. The red solid was filtered off, washed with water, and dried (42 g.; 94%). It was used without further purification for the preparation of 2-carbethoxyskatole.

2-Carbethoxyskatole.—A solution of this crude phenylhydrazone (42 g.) in a mixture of ethyl alcohol (200 c.c.) and concentrated sulphuric acid (25 c.c.) was refluxed for 45 minutes, then poured into water, and the resulting solid filtered off, washed with water, and dried. After crystallisation from methanol, the 2-carbethoxyskatole melted at 134—136° (Wislicenus and Arnold, *Annalen*, 1888, **246**, 334, give m. p. 133—134°); yield 32 g., 83%.

1-Hydroxy-2-carbethoxyskatole.—2-Carbethoxyskatole (20 g.) and acetic acid (300 c.c.) were placed in a flask fitted with a mechanical stirrer, dropping-funnel, thermometer, and gas-outlet tube. The flask was warmed in a water-bath till all the solid had dissolved, and the solution was then stirred at 50—60° while a solution of sulphuryl chloride (9·6 c.c.) in acetic acid (20 c.c.) was added fairly rapidly from the dropping-funnel. When the addition was complete, the solution was heated to 70° and kept thereat for 30 minutes. The mixture was allowed to cool slowly with stirring, and then left overnight at room temperature. Most of the acetic acid was removed in a vacuum at a low temperature,

the residue poured into a large quantity of water, and the solution extracted thoroughly with ether. The ethereal solution was washed first with sodium hydrogen carbonate solution, then with water, and dried over calcium chloride. The ether was removed, leaving an oil, which solidified after long standing in the refrigerator. Crystallisation from ether–petrol (b. p. 40—60°) gave 1-*hydroxy*-2-*carbethoxyskatole* as colourless needles, m. p. 87—88° (Found: C, 65·8; H, 6·1; N, 6·7; terminal Me, 11·1. $C_{12}H_{13}O_3N$ requires C, 65·7; H, 6·0; N, 6·4; terminal Me, 13·7%); yield 5·9 g., 27%. The compound was easily soluble in 2N-sodium hydroxide solution.

The authors wish to thank Miss V. M. Witherow for assistance in the experimental work, and Miss H. King for some of the microanalyses.

GLAXO LABORATORIES LTD., GREENFORD, MIDDLESEX. [*Received, August 16th*, 1944.]

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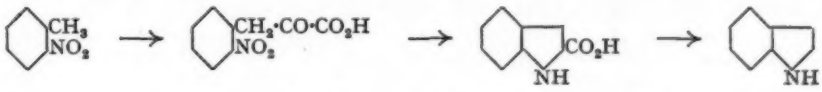
171. *Studies in the Indole Series. Part III. Improved Synthesis of Tryptophan.*

By J. ELKS, D. F. ELLIOTT, and B. A. HEMS.

Indole-3-glyoxylic acid forms an anil which is smoothly decarboxylated in anisole to a product that, after hydrolysis, gives indole-3-aldehyde in high yield. This constitutes a convenient method for preparing this aldehyde from indole. By using catalytic hydrogenation in place of other methods of reduction, two of the published methods of preparing tryptophan have been improved, enabling it to be readily prepared in moderate quantity in the laboratory.

BOYD and ROBSON (*Biochem. J.*, 1935, **29**, 2256) prepared tryptophan by reductive hydrolysis of indolylidenehydantoin with ammonium sulphide, but we found the method very inconvenient and so decided to investigate other methods of reduction and hydrolysis. For this purpose it was necessary to prepare indole and indole-3-aldehyde in quantity.

Many methods of preparing indole are known (see summaries: Van Order and Lindwall, *Chem. Rev.*, 1942, **30**, 69; Stepanov and Polyakova, *Sintezy Dushistykh. Veshchetsv Sbornik Statei*, 1939, 127; Shorygin and Polyakova, *ibid.*, 1939, 130; *Khim. Referat. Zhur.*, 1940, No. 4, 114). A recent method (Tyson, *J. Amer. Chem. Soc.*, 1941, **63**, 2024), comprising the treatment of formo-*o*-toluidide with potassium alkoxides, has been used by us on the small scale with very satisfactory results, but for preparing larger quantities of indole the use of metallic potassium is attended by obvious disadvantages. For this reason the following series of reactions was studied:



Shorygin and Polyakova (*loc. cit.*) state that this is the best method, but we have not had access to the original paper.

Of the various methods used for condensing ethyl oxalate with *o*-nitrotoluene, that suggested by Mayer and Balle (*Annalen*, 1914, **403**, 1188) proved to be the most convenient, but their method of isolation was time-consuming and tended to destroy some of the product. A more satisfactory method of isolating the product is described in the experimental section.

The reduction and cyclisation of *o*-nitrophenylpyruvic acid to indole-2-carboxylic acid was conveniently effected by sodium hyposulphite [dithionite] (Cornforth and Robinson, J., 1942, 680) or ferrous sulphate and ammonia (Kermack, Perkin, and Robinson, J., 1921, **119**, 1625). Although, however, a number of attempts were made to reduce *o*-nitrophenylpyruvic acid catalytically, with Raney nickel as catalyst, wholly satisfactory results were not obtained by this method. The required product, indole-2-carboxylic acid, was obtained from hydrogenations carried out in both alcoholic and aqueous ammonia solutions; in the latter instance some 1-hydroxyindole-2-carboxylic acid was also obtained. Some samples of the nitro-acid tended to inactivate the catalyst, and in alcoholic solutions the temperature had to be carefully controlled, since reduction did not take place at room temperature, whereas decomposition occurred at about 80°. As the chemical methods of reduction mentioned above seemed fairly satisfactory, the catalytic method was not further studied.

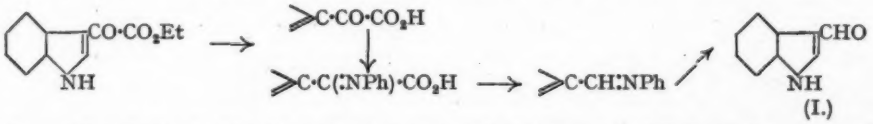
Ethyl indole-2-carboxylate was prepared in good yield on a small scale from ethyl pyruvate phenylhydrazone, prepared by reaction between ethyl methylacetoacetate and benzenediazonium chloride by treatment with a mixture of acetic and sulphuric acids, but the reaction was difficult to carry out on a larger scale.

Decarboxylation of indole-2-carboxylic acid was conveniently effected by heating, though for this purpose it was necessary that the acid should be pure and free from inorganic salts; no improvement in yield was effected by using catalysts or solvents. The above series of reactions to indole has also been studied by Cornforth and Robinson (*loc. cit.*), but they apparently used the method of Mayer and Balle without modification, and no details for the decarboxylation of indole-2-carboxylic acid are given.

Indole has been converted into its 3-aldehyde by the Reimer–Tiemann reaction (Ellinger and Flamand, *Ber.*, 1907, **40**, 3029; *Z. physiol. Chem.*, 1908, **55**, 8; Boyd and Robson, *Biochem. J.*, 1935, **29**, 555) and by reaction of indolylmagnesium iodide with ethyl formate (Majima and Kotake, *Ber.*, 1922, **55**, 3859; Potokhin, *J. Russ. Phys. Chem. Soc.*, 1927, **59**, 761; *Chem. Abs.*, 1928, **22**, 3409), but satisfactory yields were not obtained by either of these reactions. Several attempts were made to obtain the aldehyde by reaction between indole

and diphenylformamidine under various conditions, or by treating indolylmagnesium iodide with ethyl orthoformate, but these were unsuccessful.

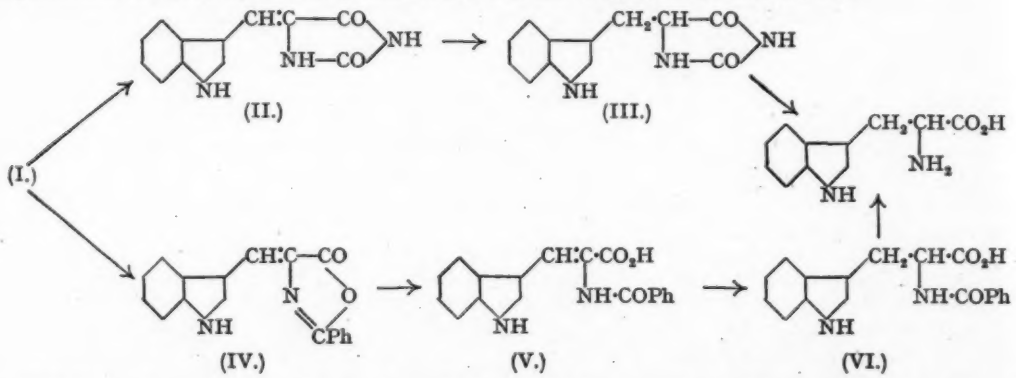
It was found that indoleglyoxylic acid readily formed an *anil* which was decarboxylated smoothly in boiling anisole to indolealdehyde anil. This was hydrolysed to indolealdehyde when the mixture was steam-distilled to remove the decarboxylation solvent. The yields at all stages were excellent, and the aldehyde so obtained was easily purified. Methyl indoleglyoxylate was first prepared from indolylmagnesium iodide and oxalic acid half ester chloride (Majima and Shigematsu, *Ber.*, 1924, **57**, 1453; Baker, J., 1940, 458), but it was later found that the ethyl ester could be readily prepared by reaction between indole and ethyl oxalate (cf. condensation of 2-methylindole with ethyl oxalate; Angeli and Marchetti, *Chem. Zentr.*, 1908, I, 739). In the presence of alcoholic sodium ethoxide, very poor yields of the glyoxylic ester were obtained; these were improved by carefully drying the reagents and by using pyridine as a catalyst in the condensation (cf. Grundmann, *Ber.*, 1937, **70**, 1148 : Blout, Fried, and Elderfield, *J. Org. Chem.*, 1943, **8**, 37). The ester after hydrolysis was converted into indole-3-aldehyde in the manner described above, the reactions being as follows :



(I.)

Condensation of the aldehyde (I) with hydantoin according to Boyd and Robson (*loc. cit.*) gave indolylidenehydantoin (II) in excellent yield, and although this substance is sparingly soluble in all solvents, a suspension in dilute sodium hydroxide solution or aqueous alcohol was readily reduced catalytically in presence of Raney nickel, to 4-3′-indolylmethylhydantoin (III), which is fairly soluble in both media; it was readily isolated in good yield by acidifying or evaporating the solution, and was obtained sufficiently pure for hydrolysis to tryptophan by baryta.

Catalytic reduction may also be applied to the preparation of tryptophan by Ellinger and Flamand's azlactone method (*loc. cit.*). The azlactone (IV), prepared according to these authors, was hydrolysed to α-benzamido-β-indole-3-acrylic acid (V), which in alkaline solution was reduced catalytically to benzoyltryptophan (VI). In this reaction Raney nickel was superior to platinum as a catalyst, since reduction with the latter was incomplete unless successive quantities of fresh catalyst were added. The hydrogenation of α-acetamidocinnamic acid with platinum oxide (Adams) catalyst, in acetic acid solution, followed by hydrolysis to phenylalanine, has been described by Herbst and Shemin (*Org. Synth.*, 1939, **19**, 67).



The dl-N-*benzoyltryptophan* so obtained was hydrolysed with concentrated baryta solution. Pure benzoyltryptophan according to Berg, Rose, and Marvel (*J. Biol. Chem.*, 1929, **85**, 207) has m. p. 104—105°, but our product, which was racemic, had m. p. 193—194°. Presumably the compound described by Berg *et al.* is not the racemic compound, since the conditions used in the benzoylation were very mild; unfortunately, the optical rotation is not recorded. The identity of the amino-acid isolated by these methods was established by colour reactions and by the preparation of the acetyl derivative, which was found to be identical in all respects with that of racemised natural tryptophan.

Experimental.

o-*Nitrophenylpyruvic Acid.*—The reaction conditions described by Mayer and Balle (*loc. cit*) were used, but their method of isolation was improved as follows : The dark red reaction mixture from *o*-nitrotoluene (1096 g.) was cooled to 0° and carefully acidified with a mixture of concentrated hydrochloric acid (800 c.c.) and water (500 c.c.), the temperature being kept below 10°. The alcohol was then removed in a vacuum at 30—40°, the oily residue dissolved in ether, and filtered from sodium chloride. The ethereal solution was then thoroughly shaken with two portions (8000 and 2700 c.c.) of ice-cold N-sodium hydroxide, and the combined alkaline extracts were washed with a little fresh ether and acidified below 10° with dilute hydrochloric acid (1 : 1). The acid was extracted with ether, the ether dried and evaporated, and the residue triturated with benzene. The crude product had m. p. 115° and was used in this state (yield 654 g.; 60% based on *o*-nitrotoluene consumed). The combined ethereal layers from the alkali extraction contained *o*-nitrotoluene (381 g.), which was recovered.

Ethyl Indole-2-carboxylate.—A mixture of ethyl pyruvate phenylhydrazone (20 g.) (Japp and Klingemann, *Ber.*,

1887, **20**, 2942; *Annalen*, 1888, **247**, 208) and a solution of concentrated sulphuric acid (7·5 c.c.) in glacial acetic acid (100 c.c.) was gently warmed to 45°, and the source of heat removed. An exothermic reaction took place, the internal temperature rising to 85°. The solution was allowed to cool to room temperature, and poured into ice-water (500 c.c.). The crude carbethoxyindole (yield, 10·6 g.; 58%), after being separated, washed, and crystallised from alcohol, had m. p. 122°, yielding indole-2-carboxylic acid, m. p. 202—204°, on hydrolysis with sodium hydroxide.

Alcoholic hydrogen chloride, alcoholic sulphuric acid, aqueous sulphuric acid, zinc chloride in alcohol, or hydrogen bromide in acetic acid under varied conditions were in some instances without effect on ethyl pyruvate phenylhydrazone; in others, decomposition occurred.

Indole-2-carboxylic Acid.—The method of Kermack, Perkin, and Robinson (*loc. cit.*) was used, but the following isolation procedure was more convenient for large-scale working. The reaction mixture from *o*-nitrophenylpyruvic acid (810 g.) after 12 hours' heating at 100° was cooled to room temperature and acidified, with stirring, with concentrated hydrochloric acid (10·8 l.), the temperature being allowed to rise to 50°, but not above. After standing overnight, the brown solid was filtered off, washed with water, and purified by dissolving it in an excess of hot 2N-ammonia, filtering, cooling, and acidifying the filtrate with dilute hydrochloric acid (1 : 1). The buff precipitate was filtered off, washed, and dried; a further quantity of acid was obtained from the filtrate by ether extraction. The crude product had m. p. 190—194°; yield 378 g., 60·6%.

Indole.—For successful decarboxylation it was necessary to use pure indole-2-carboxylic acid; impure acid gave very low yields. The acid described above was decolorised with charcoal and crystallised from aqueous alcohol. It had m. p. 203°. The purified acid (1000 g.) was heated at 240° in a 4-l. flask fitted with a long air-condenser until decarboxylation ceased (1¼ hours). The mass was then cooled and distilled in a vacuum. Indole distilled as a colourless liquid, b. p. 120°/2—3 mm., which rapidly solidified in the receiver. It was further purified by pouring when molten into ice-cold, well-stirred petroleum (1600 g., b. p. 80—100°). After standing for 12 hours at 0°, the indole was filtered off and dried (400 g., 55%); m. p. 51—52°.

Ethyl Indole-3-glyoxylate.—A number of modifications of the reaction procedure were investigated; the following gave the best results. To a solution of sodium (20 g.) in alcohol (250 c.c.; 0·03% H_2O) were added pyridine (dried over barium oxide; 50 c.c.), ethyl oxalate (70 g.), and indole (50 g.). The mixture was then heated on the steam-bath for 4 hours, with exclusion of moisture, cautiously at first because of frothing. The dark brown solution was then cooled to room temperature and poured, with stirring, on crushed ice (300 g.) and 2N-hydrochloric acid (800 c.c.). The yellowish-brown solid was filtered off, washed with water, dried in a vacuum over concentrated sulphuric acid, powdered, and washed thoroughly with cold ether to remove tarry impurities. The air-dried solid had m. p. 176—178° (48 g.; 50%) and was pure enough for subsequent work.

Indole-3-glyoxylic Acid Anil.—For the preparation of this compound it is preferable to use the glyoxylic acid in a moist condition. The quantity of acid to be expected from the crude ethyl indoleglyoxylate was therefore first estimated by hydrolysing a small portion by warming to 40° with five times its weight of 2N-sodium hydroxide solution. The ester rapidly dissolved, and after it had stood for ½ hour at room temperature, charcoal was added to remove a small quantity of tar, and the solution was filtered and acidified with hydrochloric acid (1 : 1). The canary-yellow precipitate was filtered off, washed, dried, and crystallised from ethyl acetate. The pure acid had m. p. 215° (decomp.), not depressed on admixture with a specimen of the acid prepared by Baker's method (*loc. cit.*).

Ethyl indole-3-glyoxylate (48 g., equivalent to 33·4 g. of acid) was hydrolysed as above, and the precipitated acid, after filtration (pump) and thorough washing with water, was added to a mixture of aniline (16·7 g.) and water (167 c.c.). The suspension was shaken and heated at 100° until a clear solution was formed. After cooling, the pink crystals were filtered off and dried in a vacuum. The *anil* had m. p. 180° (decomp.) after softening at 140° (yield 47 g., 80% calc. on crude ester) (Found: N, 10·4. $C_{16}H_{12}O_2N_2$ requires N, 10·6%).

Indole-3-aldehyde.—The anil (47 g.) was mixed with anisole (188 c.c.) and heated at about 140° (oil-bath) until evolution of carbon dioxide subsided. The mixture was then refluxed until the solid matter dissolved and gas evolution ceased (1 hour). After cooling, the brown solution was diluted with water (200 c.c.), and anisole and aniline removed by steam-distillation. The liquid then remaining was cooled, and the aldehyde (24 g.; 93%) filtered off and dried. The aldehyde, after crystallisation from aqueous alcohol, had m. p. 198°, not depressed on admixture with an authentic specimen.

4-3′-Indolylmethylhydantoin.—(a) Indolylidenehydantoin, prepared from indole-3-aldehyde by Boyd and Robson's method (*loc. cit.*) (5 g.), was suspended in N-sodium hydroxide (50 c.c.) and hydrogenated at room pressure and temperature in presence of Raney nickel catalyst (5 g.). The solid dissolved during the hydrogenation, which was complete in 8 hours. The catalyst was filtered off, and the filtrate acidified with dilute hydrochloric acid. The colourless, crystalline precipitate (5 g.) had m. p. 214° and was sufficiently pure for hydrolysis to tryptophan. A sample, crystallised from water, had m. p. 218—220°. Majima and Kotake (*Ber.*, 1922, **55**, 3859) prepared this substance by sodium amalgam reduction of indolylidenehydantoin and gave m. p. 220—221°.

(b) Indolylidenehydantoin (20 g.), suspended in aqueous alcohol (65% EtOH; 200 c.c.), was shaken with hydrogen at 100—110° and 50 atm., in presence of Raney nickel (20 g.) for 2 hours. The reaction mixture was allowed to cool to 80° with continued shaking, and then filtered hot and the catalyst washed with hot 65% alcohol. The filtrate was evaporated to small bulk, giving a crystalline residue (16·3 g.; 80%), m. p. 218°, of 4-3′-indolylmethylhydantoin.

dl-N-*Benzoyltryptophan.*—*α*-Benzamido-*β*-indole-3-acrylic acid (Ellinger and Flamand, *loc. cit.*) (35 g.), dissolved in N-sodium hydroxide (350 c.c.), was hydrogenated at room temperature and pressure in presence of Raney nickel (17 g.). When hydrogenation was complete (5 hours), the catalyst was filtered off, washed with water, and the filtrate cautiously acidified with dilute hydrochloric acid. The pink solid (34 g.; 96·5%) had m. p. 193—194° after crystallisation from aqueous alcohol. Difficulty was experienced in obtaining a pure sample of this *substance*, for it rapidly became pink on heating in solvents (Found: C, 69·5; H, 5·1; N, 8·7. $C_{18}H_{16}O_3N_2$ requires C, 70·1; H, 5·2; N, 9·1%).

dl-*Tryptophan.*—(a) 4-3′-Indolylmethylhydantoin (13·8 g.), barium hydroxide (cryst., 69 g.), and water (420 c.c.) were mixed and refluxed for 24 hours. The solution evolved ammonia and deposited barium carbonate. The condenser was then removed, and steam allowed to escape to expel the last traces of ammonia. After dilution of the solution to 1200 c.c., it was heated on the steam-bath, and a rapid stream of carbon dioxide passed in until the supernatant liquor was neutral to litmus. The barium carbonate, thus obtained in granular form, was filtered off and washed with boiling water (300 c.c.); the filtrate was freed from the last trace of barium ions by addition of 2N-sulphuric acid (rhodizonic acid indicator). After a further filtration the solution was evaporated to dryness in a vacuum. The residue of tryptophan (11·1 g., 90%) was washed with alcohol and dried. The m. p. was 284° (decomp.) with darkening from 260° (Found: C, 64·8; H, 5·9; N, 13·4. Calc. for $C_{11}H_{12}O_2N_2$: C, 64·7; H, 5·9; N, 13·7%). The overall yield (72%) on indolylidenehydantoin is the same as that recorded by Boyd and Robson (*loc. cit.*).

(b) *dl-N*-Benzoyltryptophan (finely powdered, 30 g.) was hydrolysed as above with barium hydroxide (165 g.) and water (900 c.c.). After removal of barium ions with 2N-sulphuric acid, the filtered solution was evaporated to dryness in a vacuum, and the residue washed with alcohol to remove benzoic acid. The pale yellow product (15 g., 75%), m. p. 274°, after crystallisation from hot water, had m. p. 282° (decomp.) with darkening from 260° (Found C, 64·7; H, 6·0;

N, 13·3%). The yield of tryptophan from α-benzamido-β-indole-3-acrylic acid is 72%, whereas Ellinger and Flamand (*loc. cit.*) recorded a 15% yield by reduction with sodium in alcohol.

The colours obtained with the Ehrlich and the Hopkins–Cole reagent from the two samples of tryptophan were identical with those obtained from natural tryptophan. The acetyl derivatives, prepared by the method of Berg, Rose, and Marvel (*loc. cit.*) from the above samples of tryptophan, had m. p. 203°, alone or on admixture with an authentic specimen of *dl*-*N*-acetyltryptophan, m. p. 203°, prepared from natural tryptophan.

The authors wish to thank Mr. A. R. Bone for details of a large-scale preparation of indole, and Miss M. A. Smith and Mr. G. J. Waller for assistance in some of the experimental work. Thanks are also due to Mr. F. A. Robinson for his interest in the work described in these papers.

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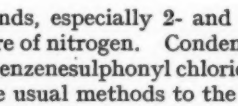
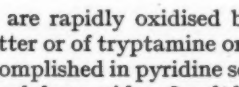
172. *Studies in the Indole Series. Part IV. Sulphonamides derived from Indole.*

By D. F. ELLIOTT and F. A. ROBINSON.

Three new sulphonamides containing the indole nucleus have been prepared, namely, 3-sulphanilamidoethylindole, 3-sulphanilamidoindole, and 5-sulphanilamido-2 : 3-dimethylindole. These showed moderate antibacterial activity, but were very sparingly soluble in water.

IN continuation of the work on indole compounds, it appeared to be of interest to prepare and study the properties of sulphonamides containing the indole nucleus. Up to the present, efforts have been restricted to the condensation of *p*-acetamidobenzenesulphonyl chloride with the most readily accessible indole amines. These are β-3-indolylethylamine (I) (tryptamine) (Majima and Hoshino, *Ber.*, 1925, **58**, 2045), 2-aminoindole (Pschorr and Hoppe, *Ber.*, 1910, **43**, 2550), 3-aminoindole (Madelung, *Annalen*, 1914, **405**, 92), and 5-amino-2 : 3-dimethylindole (Bauer and Strauss, *Ber.*, 1932, **65**, 308).

(I.)  (II.) 

These amino-compounds, especially 2- and 3-aminoindole, are rapidly oxidised by air and they are best prepared in an atmosphere of nitrogen. Condensation of the latter or of tryptamine or 5-amino-2 : 3-dimethylindole with *p*-acetamidobenzenesulphonyl chloride is readily accomplished in pyridine solution, and the products can be hydrolysed by the usual methods to the corresponding sulphonamides, *3-sulphanilamidoethyl-*, *3-sulphanilamido-*, and *5-sulphanilamido-2 : 3-dimethyl-indole*.

Several unsuccessful attempts were made to condense 2-aminoindole with *p*-acetamidobenzenesulphonyl chloride in presence of pyridine or aqueous sodium hydroxide solution. Reaction of indole-2-urethane (II) (Piccinini and Salmoni, *Gazzetta*, 1902, **32**, I, 252) with *p*-acetamidobenzenesulphonyl chloride also failed to yield a product that could be characterised. In both these reactions highly coloured tars of unknown composition were produced.

The new sulphonamides proved to be very sparingly soluble in water, and this made it difficult to test them for antibacterial activity. For the *in vitro* tests it was necessary to use strongly alkaline solutions (pH 10—12) with the risk of precipitation when these were added to the medium. Even under these conditions, using a synthetic medium, 3-sulphanilamidoethyl- and 3-sulphanilamido-indole inhibited the growth of *Streptococcus hæmolyticus* at a dilution of 1 in 50,000, and 5-sulphanilamido-2 : 3-dimethylindole at a dilution of 1 in 500,000. Suspensions of these compounds were administered orally to mice infected with *Pneumococcus* and *Streptococcus hæmolyticus*; 3-sulphanilamido- and 5-sulphanilamido-2 : 3-dimethyl-indole appeared to prolong the life of the animals for a few days, but the effect was not sufficiently marked to warrant further investigation.

EXPERIMENTAL.

The indole amines (1 g.) were condensed with the theoretical quantity of *p*-acetamidobenzenesulphonyl chloride in cold pyridine solution (dried over barium oxide; 10 c.c.) in an atmosphere of nitrogen, and after standing overnight, the reaction mixtures were poured on ice and 2N-hydrochloric acid. The following data were obtained for the acetyl sulphonamides : *3-Acetylsulphanilamidoethylindole*, dense crystals from ethyl acetate, m. p. 134° (yield 66%) (Found : C, 60·4; H, 5·2; N, 11·75; S, 8·4. $C_{18}H_{19}O_3N_3S$ requires C, 60·5; H, 5·4; N, 11·8; S, 9·0%). *3-Acetylsulphanilamidoindole*, dense yellow prisms from acetone, m. p. 248—250° (decomp.) (yield 92%) (Found : C, 58·5; H, 4·8; S, 9·8. $C_{16}H_{15}O_3N_3S$ requires C, 58·4; H, 4·6; S, 9·7%). *5-Acetylsulphanilamido-2 : 3-dimethylindole*, dense prisms from acetone, m. p. 266—267° (decomp.) (yield 96%) (Found : C, 60·7; H, 5·35; N, 11·6; S, 9·1. $C_{18}H_{19}O_3N_3S$ requires C, 60·5; H, 5·4; N, 11·8; S, 9·0%).

The sulphonamides were prepared from their acetyl derivatives as follows : *3-Sulphanilamidoethylindole*. The acetyl compound (1 g.) was refluxed for 15 minutes with a mixture of concentrated hydrochloric acid (3 c.c.) and water (6 c.c.). A mass of the sparingly soluble hydrochloride of the free base was produced, and was decomposed by addition of excess of aqueous ammonia to the warm solution. The free *base* was filtered off, and crystallised from ethyl acetate and then from aqueous alcohol after treatment with charcoal, to give sheaves of needles, m. p. 143—144° (Found : C, 61·1; H, 5·5; N, 13·0; S, 10·2. $C_{16}H_{17}O_3N_3S$ requires C, 60·9; H, 5·4; N, 13·3; S, 10·2%). *3-Sulphanilamidoindole*. The acetyl compound (0·3 g.) was refluxed with 2N-sodium hydroxide (2 c.c.) for 15 minutes. The cooled solution was diluted with water (2 c.c.) and made faintly acid with dilute acetic acid. The precipitate was filtered off and crystallised several times from alcohol after treatment with charcoal. The *sulphonamide* formed plates with a pink tinge, m. p.

219—220° (decomp.) (Found: C, 58·6; H, 4·8; N, 14·3; S, 10·9. $C_{14}H_{13}O_2N_3S$ requires C, 58·5; H, 4·6; N, 14·6; S, 11·2%). *5-Sulphanilamido-2 : 3-dimethylindole.* The acetyl compound (1 g.) was refluxed for 30 minutes with 2N-sodium hydroxide (7 c.c.), cooled, and the solution acidified with dilute acetic acid. The crude product was dissolved in excess of hot 2N-hydrochloric acid, filtered, and the filtrate neutralised with sodium carbonate. The free *base*, crystallised from alcohol, formed needles, m. p. 243—244° (Found: C, 60·8; H, 5·5; N, 13·05; S, 10·05. $C_{16}H_{17}O_2N_3S$ requires C, 60·9; H, 5·4; N, 13·3; S, 10·2%).

The antibacterial tests mentioned in this paper were carried out in the Department of Experimental Medicine under the direction of Dr. J. Ungar, to whom the authors' thanks are due.

GLAXO LABORATORIES, LTD., GREENFORD, MIDDLESEX. [*Received, August 16th*, 1944.]

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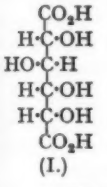
173. *Lactones of Glucosaccharic Acid. Part III. Mono- and Di-lactones.*

By F. SMITH.

Sohst and Tollens's saccharolactone (*Annalen*, 1888, **245**, 1, 19), now obtained directly from potassium hydrogen saccharate, is a mixture of glucosaccharo-1 : 4-lactone (II; R = H) and glucosaccharo-3 : 6-lactone (V; R = H). These two monolactones have been separated and their structures proved by conversion into known crystalline derivatives. They have been transformed respectively into the dilactones (X) and (IX), both of which reduce Fehling's solution.

In a previous communication (this vol., p. 571) evidence was put forward which indicated that the so-called saccharolactone (m. p. 133°) of Sohst and Tollens, originally assumed to be a 3 : 6-monolactone (V; R = H), is a mixture of this with a 1 : 4-monolactone (II; R = H). Confirmation of this view was effected by the separation and identification of these two monolactones.

The syrupy mixture of the monolactones of glucosaccharic acid which gradually crystallises on keeping in air at room temperature was extracted with cold acetone. This procedure removed the 1 : 4-lactone, leaving the 3 : 6-lactone. Pure specimens of the latter show m. p. 149°, $[\alpha]_D$ +45° (Sohst and Tollens, *loc. cit.*; Rehorst and Scholz, *Ber.*, **1936**, **69**, 524, record m. p. 130—132°, $[\alpha]_D$ +38° for this substance). The saccharo-1 : 4-lactone can be separated from the acetone extract as a crystalline monohydrate, m. p. 98°, $[\alpha]_D$ +32·5° (cf. Reichstein, *Helv. Chim. Acta*, 1939, **22**, 4).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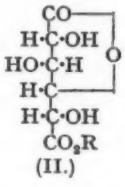
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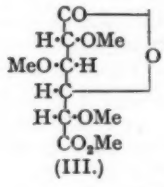
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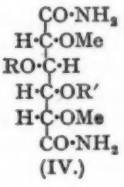
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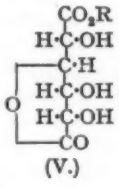
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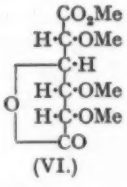
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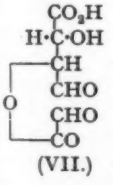
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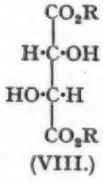
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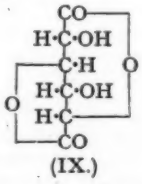
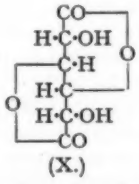
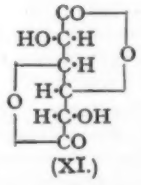

(IX.)


(X.)


(XI.)

The structure (II; R = H) assigned to this monohydrate (m. p. 98°) is based upon the following facts: The monolactone showed relatively slow mutarotation in aqueous solution, typical of the γ-lactones in the glucose series. Reduction of (II; R = H) with sodium amalgam affords glucuronic acid (Fischer and Piloty, *Ber.*, 1891, **24**, 522; Reichstein, *loc. cit.*), and since it is the carbonyl group of the lactone ring and not that of the carboxyl group which is transformed into the reducing group of glucuronic acid, then in the monolactone (II; R = H) it must be C_1 and not C_6 which is engaged in the lactone ring. This monolactone does not react with periodic acid under conditions which easily effect disruption of the carbon chain of the glucosaccharo-3 : 6-lactone (see below). This suggests that (II; R = H) does not contain adjacent *cis*-hydroxyl groups. Titration of (II; R = H) with an ethereal solution of diazomethane yielded a crystalline methyl ester (II; R = Me); when this was treated with silver oxide and methyl iodide it afforded crystalline 2 : 3 : 5-trimethyl glucosaccharo-1 : 4-lactone 6-methyl ester (III). The latter, obtainable also by direct methylation of the monolactone (II; R = H) with silver oxide and methyl iodide, was further characterised by its conversion into the corresponding diamide (IV; R = Me, R′ = H). Both the ester (III) and this amide were identical with specimens previously prepared by methylation of the crude mixture of monolactones (II; R = H) and (V; R = H), and with specimens prepared synthetically from glucose (Smith, this vol., p. 571). The structure (II; R = H) given to the glucosaccharo-1 : 4-lactone monohydrate is therefore correct.

The monolactone (m. p. 149°) to which was assigned the structure (V; R = H) behaves like the 1 : 4-monolactone in that it exhibits slow mutarotation in aqueous solution, thus indicating the presence of a γ- and not a δ-lactone ring. Reduction of (V; R = H) in neutral or slightly acid solution has been shown to give rise to

guluronic acid (Reichstein, *loc. cit.*), a fact which proves that the carboxyl group at C_6 must be engaged in the lactone ring. Titration of (V; R = H) with an ethereal solution of diazomethane causes rapid esterification of the carboxyl group and there is formed the crystalline glucosaccharolactone methyl ester (V; R = Me) (cf. Reeves, *J. Amer. Chem. Soc.*, **1939**, **61**, 664). This ester, like the glucosaccharo-1 : 4-lactone 6-methyl ester, reduces boiling Fehling's solution. [The explanation of the reducing activity of these ester lactones and that shown by the two dilactones (IX) and (X) will be advanced in a subsequent communication.] Methylation of (V; R = Me) with silver oxide and methyl iodide gives the trimethyl glucosaccharolactone methyl ester (VI), which is converted into the known diamide (IV; R = H, R′ = Me) of 2 : 4 : 5-trimethyl glucosaccharic acid identical with that previously prepared from the mixture of monolactones of saccharic acid (Smith, *loc. cit.*). Confirmation of the structure assigned to the monolactone (m. p. 149°) was forthcoming from an examination of its reactions with periodic acid (Malaprade, *Bull. Soc. chim.*, **1928**, **43**, 683; **1934**, **1**, 833; Herrissey, Fleury, and Joly, *J. Pharm. Chim.*, **1934**, **20**, 149; Schmidt and Gunthert, *Ber.*, **1938**, **71**, 493; Reeves, *loc. cit.*). This reagent effects scission of the carbon chain between C_4 and C_5 to give the dialdehyde (VII), which is readily oxidised by bromine to oxalic acid and dihydroxy-*l*-threosuccinic acid (*d*-tartaric acid) (VIII; R = H), identified in the form of its crystalline methyl ester (VIII; R = Me).

Inspection of the structures (II; R = H) and (V; R = H) allocated to the two monolactones of glucosaccharic acid shows that each should be capable of giving rise to a dilactone. This proved to be the case: when the 3 : 6-lactone is subjected to prolonged heating in a vacuum it melts gradually, water is eliminated, and a dilactone (m. p. 135°) believed to have the structure (IX) crystallises spontaneously. This dilactone exhibits relatively rapid mutarotation in aqueous solution ($[\alpha]_D$ +166° changing in 22 hours to +44°). The specific rotation of an aqueous solution of the dilactone at equilibrium is almost identical with that of a freshly prepared solution of the 3 : 6-lactone. This fact, together with the observation that removal of the solvent from the equilibrium solution at a low temperature affords the original saccharolactone (V; R = H), shows that the dilactone contains the 3 : 6-γ-lactone ring. The relatively rapid mutarotation of the dilactone suggests, but does not prove, that its second lactone ring is of the δ-type and that it engages C_1 and C_5 (see below). Hence the formula (IX) was tentatively assigned to this dilactone (cf. Rehorst and Scholz, *Ber.*, **1936**, **69**, 524).

Similarly, it has been demonstrated that when the monohydrate of saccharo-1 : 4-lactone (II; R = H) is heated in a vacuum above its m. p. the water of crystallisation is first eliminated and a second ring is introduced into the molecule. The stereochemical arrangement of the hydroxyl groups at C_2 and C_3 is such as to allow of the formation of a lactone ring only between the hydroxyl group at C_3 and the carboxyl group at C_6. The formation of a δ-lactone ring between C_6 and C_2 of (II; R = H) would involve so much strain that such a possibility can be ruled out. The only possible configuration for this dilactone is therefore (X), in which both the lactone rings are of the γ-type. This new glucosaccharodilactone thus has a configuration analogous to that assigned to mannosaccharodilactone (XI), which likewise possesses two γ-lactone rings (Schmidt and Kraft, *Ber.*, **1941**, **74**, 33; Heslop and Smith, this vol., p. 574). Support for the presence of the 3 : 6-lactone ring in (X) is provided by the fact that evaporation of an aqueous solution of the dilactone, which has mutarotated and reached equilibrium, gives glucosaccharo-3 : 6-lactone (V; R = H). The introduction of the 3 : 6-lactone ring in the conversion of the monolactone (II; R = H) ($[\alpha]_D$ +32·5° for the monohydrate) into the dilactone (X) ($[\alpha]_D$ +144°) is also borne out by the fact that the formation of the dilactone is accompanied by an enhancement of the rotation in the positive direction. If the second lactone ring in (X) were of the δ-type, joining C_6 to C_2, its formation would be expected to be accompanied by a rotational change in the negative sense. Since the two dilactones, derived from the 3 : 6- and the 1 : 4-glucosaccharolactone respectively, are different, it follows that the second ring introduced into the 3 : 6-monolactone in the formation of the corresponding dilactone must engage C_1 and C_5, for if it involved C_1 and C_4 then it would be identical with the dilactone obtained from saccharo-1 : 4-lactone.

It is noteworthy that the dilactone (IX) derived from glucosaccharo-3 : 6-lactone (V; R = H) is given a formula in which one lactone ring is of the δ-type, chiefly because it shows rapid mutarotation in aqueous solution. On the other hand, the dilactone obtained from glucosaccharo-1 : 4-lactone (II; R = H), and given the structure (X) because of stereochemical considerations and the fact that (X) has a higher positive rotation than (II; R = H), also shows relatively rapid mutarotation. This similarity of the mutarotation of these two dilactones is difficult to reconcile with the structure (X) given to the dilactone, especially when one considers that mannosaccharodilactone (XI), which has two γ-lactone rings (Schmidt and Kraft, *Ber.*, **1941**, **74**, 33), shows very slow mutarotation. The apparent anomaly may be partly due to the strain in such dicyclic systems caused by the interlocking rings (see Haworth, Jackson, and Smith, J., **1940**, 620; Haworth, Owen, and Smith, J., **1941**, 88), and partly to the spatial configuration of the other groups in the molecules, *e.g.*, the hydroxyl group at C_2. Until conditions permit further studies to be made of derivatives of these dilactones of saccharic acid and other dilactones, formulæ (IX) and (X) are put forward tentatively.

Experimental.

Glucosaccharo-3 : 6-lactone (V; R = H) *and Glucosaccharo-1 : 4-lactone* (II; R = H).—A solution of potassium hydrogen saccharate (68 g.), obtained from glucose by oxidation with nitric acid, in water (100 c.c.), was treated with 5N-sulphuric acid (55 c.c., 1 equiv.). The solution was evaporated to dryness under diminished pressure at 50—60°, the residue extracted with methyl alcohol at room temperature, and the extract filtered. The filtrate was concentrated to small bulk under reduced pressure, and the concentrate, while still containing some methyl alcohol, set aside in a dish at room temperature. After 1—2 weeks the resulting crystalline mass was triturated with acetone, the residue collected,

and washed with acetone. The residue (25 g.) of saccharo-3 : 6-lactone (V; R = H) recrystallised from acetone–light petroleum; when pure, it has m. p. 149°, $[\alpha]_D^{20°}$ +45° in water (*c*, 0·9); +44° (5 days); +39·5° (15 days); +32·4° (60 days) (Found: C, 37·8; H, 4·3. Calc. for $C_6H_8O_7$: C, 37·5; H, 4·2%).

Concentration of the above acetone filtrate gave a syrup, from which a further yield of saccharo-3 : 6-lactone was obtained. Reconcentration of the acetone mother-liquors to a small volume, followed by transference to an open dish from which the residual acetone slowly evaporated, gave large crystals of saccharo-1 : 4-lactone. These were removed, washed with a little ice-cold acetone, and then recrystallised from acetone–ethyl acetate, or better, from acetone alone. The saccharo-1 : 4-lactone monohydrate thus obtained had m. p. 98° (sintering at 85°), $[\alpha]_D^{20°}$ +34° (initial value in water, *c*, 1·5); +33° (1 day); +20° (22 days). Further crops of the monohydrate were obtained from the mother-liquors (Found: C, 34·9; H, 4·8. Calc. for $C_6H_8O_7,H_2O$: C, 34·3; H, 4·8%).

Glucosaccharo-1 : 4-*lactone* 6-*Methyl Ester* (II; R = Me).—A solution of the lactone (0·2 g.) in acetone (10 c.c.) was cooled in ice and titrated with an ice-cold ethereal solution of diazomethane until the latter was in slight excess as indicated by the persistence of a yellow colour. Immediate evaporation of the solvent under diminished pressure at 30—35° afforded the crystalline 6-methyl ester in almost quantitative yield, m. p. 165° (after recrystallisation from ethyl alcohol). The crystals dissolve in water to give a neutral solution showing $[\alpha]_D^{18°}$ +24° in water (*c*, 0·5), but on keeping, the aqueous solution becomes slightly acid to litmus and Congo-red paper. The methyl ester reduces Fehling's solution on boiling (Found: C, 41·0; H, 5·0; OMe, 15·2. Calc. for $C_7H_{10}O_7$: C, 40·8; H, 4·9; OMe, 15·05%).

Methylation of the Methyl Ester (II; R = Me).—A solution of this ester (0·9 g.) in the minimum amount of acetone was allowed to react with methyl iodide (5 c.c.) and silver oxide (4 g.) during 8 hours at 45—50°; the silver oxide was added in small amounts within 4 hours of the commencement of the methylation. The solution was filtered, and the residue washed well with hot acetone. Removal of the solvent afforded a syrup which was not completely soluble in methyl iodide. The product was therefore subjected to another treatment with silver oxide and methyl iodide in the presence of acetone. The product, isolated in the same manner, was then completely soluble in methyl iodide, and two additional similar methylations effected complete methylation. The product, isolated by means of acetone, crystallised spontaneously. Trituration of the crystalline material with ethyl alcohol–ether, followed by filtration and recrystallisation from ethyl alcohol, gave 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester (0·3 g.), m. p. 87°, $[\alpha]_D^{20°}$ +91·5° in water (*c*, 1·4).

Removal of the solvent from the mother-liquors gave a syrupy residue which upon distillation under 0·04 mm. (bath temps.) yielded: Fraction (I) (0·05 g.), b. p. 100°, $n_D^{19°}$ 1·4440; fraction (II) (0·49 g.), b. p. 135—145°, $n_D^{19°}$ 1·4550—1·4595; fraction (III) (0·11 g.), b. p. >145°, $n_D^{19°}$ 1·4640. Fraction (I) was mainly methylated tartaric acid, but fraction (III) proved to be almost pure 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester, m. p. and mixed m. p. 87° (after recrystallisation from ethyl alcohol). Fraction (II) also crystallised, and trituration with ether afforded 2 : 5-dimethyl Δ^4-glucosaccharolactone methyl ester (0·2 g.), and from the mother-liquors of this fraction a syrup was obtained which readily crystallised upon nucleation with a synthetic specimen of 2 : 3 : 5-trimethyl saccharolactone methyl ester. After recrystallisation from acetone–ether the 2 : 3 : 5-trimethyl glucosaccharolactone 6-methyl ester had m. p. 79° alone or in admixture with an authentic specimen; $[\alpha]_D^{20°}$ −12° in water (*c*, 3·0) (Found: C, 48·4; H, 6·9; OMe, 49·2. Calc. for $C_{10}H_{16}O_7$: C, 48·4; H, 6·45; OMe, 50·0%).

Methylation of Glucosaccharo-1 : 4-*lactone* (II; R = H).—A solution of glucosaccharo-1 : 4-lactone monohydrate (0·25 g.) in acetone (2 c.c.) was boiled for 8 hours under reflux with methyl iodide (3 c.c.) in the presence of silver oxide (*ca.* 2 g.), the latter being added in small portions during the first 4 hours. The product, after isolation by means of acetone, was soluble in methyl iodide and so was given two more methylations as before but without addition of acetone. Distillation of the syrupy product gave a fairly mobile, colourless oil (0·22 g.), b. p. 140°/0·02 mm., $n_D^{17°}$ 1·4520. The distillate crystallised immediately upon nucleation with a crystal of 2 : 3 : 5-trimethyl glucosaccharolactone methyl ester, and after recrystallisation from ethyl alcohol–ether–light petroleum, the 2 : 3 : 5-trimethyl glucosaccharolactone methyl ester had m. p. and mixed m. p. 79° (Found: OMe, 49·5%). 0·02 G. of distillate, b. p. (bath temp.) approx. 160°/0·02 mm., was collected after this ester, and readily crystallised on nucleation with a specimen of 2 : 5-dimethyl Δ^4-glucosaccharolactone methyl ester; after recrystallisation from ethyl alcohol–ether, it had m. p. and mixed m. p. 87°.

2 : 3 : 5-*Trimethyl Glucosaccharic Acid Diamide* (IV; R = Me, R′ = H).—A solution of 2 : 3 : 5-trimethyl saccharolactone methyl ester (0·1 g.) in dry methyl alcohol (2 c.c.) was cooled in ice, saturated with dry ammonia, and kept for 2 days at −5°; removal of the excess of the solvent in a vacuum at room temperature then yielded crystalline 2 : 3 : 5-trimethyl glucosaccharic acid diamide, m. p. 213°, $[\alpha]_D^{17°}$ +18·5 in water (*c*, 2·0) (after crystallisation from ethyl alcohol–ether). This diamide showed a negative Weerman reaction (tested on 20 mg.).

Treatment of Glucosaccharo-1 : 4-*lactone* (II; R = H) *with Periodic Acid.*—A solution of the lactone monohydrate (1 g.) in water (10 c.c.) was treated with periodic acid (1·14 g.) (80% pure) in water (15 c.c.) for 1 hour at room temperature. Hydriodic acid (39 c.c.; 0·62N) and sulphuric acid (5 c.c.; 1·05N) were then stirred in, the iodine precipitated was filtered off, and that remaining in solution was extracted with chloroform. The solution, after evaporation under diminished pressure for a short time to remove chloroform, showed no reducing activity towards Fehling's solution. The solution was neutralised with dilute potassium hydroxide, evaporated to 20—30 c.c., and treated with a slight excess of glacial acetic acid. The precipitate of potassium hydrogen saccharate was filtered off, and washed with ice-cold water; yield 0·8 g.

Glucosaccharo-3 : 6-*lactone* 1-*Methyl Ester* (V; R = Me).—A solution of the lactone (4·26 g.) in acetone (200 c.c.) was cooled in ice and titrated with an ice-cold ethereal solution of diazomethane until a permanent yellow colour persisted. The esterification proceeded smoothly and rapidly, and was accompanied by the brisk evolution of nitrogen. Removal of the excess of the solvent and diazomethane by distillation in a vacuum at 25—30° gave a crystalline residue, which was crystallised from ethyl alcohol. The glucosaccharo-3 : 6-lactone 1-methyl ester thus produced (3·0 g.) had m. p. 115°, $[\alpha]_D^{18}$ +30° in water (*c*, 1·0) (Found: C, 41·0; H, 5·0; OMe, 15·0; equiv., 102. Calc. for $C_7H_{10}O_7$: C, 40·8; H, 4·9; OMe, 15·05%; equiv., 103). It can be kept unchanged in a sealed tube, but is extremely sensitive to traces of moisture which hydrolyse it with elimination of the ester methoxyl group. Hence, when an aqueous solution of the ester had been kept for 5 weeks at room temperature, removal of the water at room temperature in a vacuum gave crystalline glucosaccharo-3 : 6-lactone, m. p. and mixed m. p. 149° (after recrystallisation from methyl alcohol–acetone) (Found: OMe, nil). Glucosaccharo-3 : 6-lactone 1-methyl ester reduces boiling Fehling's solution actively, especially if the crystalline ester is added to the hot Fehling's solution.

Methylation. A solution of the glucosaccharolactone methyl ester (2·9 g.) in the minimum volume of acetone was boiled under reflux with methyl iodide (5 c.c.) and silver oxide (5 g.) for 8 hours. The silver oxide was added in small quantities during the first 4 hours of the reaction. The syrupy product, isolated by means of acetone, was not completely soluble in methyl iodide. After a second methylation carried out under the same conditions complete solution in methyl iodide was attained. Thereafter the product was given three more methylations with methyl iodide (8 c.c.) and silver oxide (5 g.) at 40—45° during 8 hours. This procedure afforded a mixture of syrup and crystals which was triturated with ether–ethyl alcohol and filtered. These crystals, 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester (0·7 g.), had m. p. and mixed m. p. 87°, $[\alpha]_D^{20°}$ +94° in water (*c*. 2·0) (after recrystallisation from ethyl alcohol). The

syrup obtained from the mother-liquors was distilled under 0·03 mm. (bath temps.), giving: Fraction I (0·87 g.), b. p. 138°, $n_D^{20°}$ 1·4568; fraction II (0·99 g.), b. p. 150—155°, $n_D^{20°}$ 1·4645; fraction III (0·1 g.), b. p. 155—200°, $n_D^{20°}$ 1·4690. Fractions II and III crystallised almost completely upon nucleation with 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone methyl ester, and after recrystallisation from ethyl alcohol the crystals had m. p. and mixed m. p. 87°.

Fraction I gave 2 : 5-dimethyl Δ^4-glucosaccharolactone methyl ester (0·2 g.), m. p. 87° (after crystallisation from ethyl alcohol). The syrup obtained from the mother-liquors of this fraction failed to crystallise. Treatment of a portion (0·1 g.) of the syrup with methyl-alcoholic ammonia for 3 days at −5°, followed by removal of the excess of the solvent, furnished crystalline 2 : 4 : 5-trimethyl glucosaccharic acid diamide (IV; R = H, R′ = Me), m. p. 195°, $[\alpha]_D^{20°}$ +22° in water (*c*, 0·9) (after recrystallisation from water) (Found: C, 43·2; H, 7·4; N, 11·05; OMe, 37·7. Calc. for $C_9H_{18}O_6N_2$: C, 43·2; H, 7·2; N, 11·2; OMe, 37·2%). A Weerman test carried out upon this diamide (20 mg.), according to the conditions previously employed, was negative. A control test upon gluconamide (20 mg.) readily gave hydrazodicarbonamide (10 mg.), m. p. and mixed m. p. 258° (decomp.). As a further control, a Weerman test was carried out upon the diamide of 2 : 4-dimethyl mucic acid; this was positive (see Smith, J., 1939, 1724).

Treatment of Glucosaccharo-3 : 6-lactone with Periodic Acid.—To a solution of the lactone (1 g., m. p. 149°) in water (20 c.c.) cooled in ice, was added an ice-cold solution of periodic acid (1 g.; 1 mol.) in water (10 c.c.). After 10 minutes at 0°, the reaction mixture was treated with hydriodic acid (2·0 c.c., 5 mols.) followed by N-sulphuric acid (6 c.c.). The solution was worked up as in the oxidation of (II; R = H), and the resulting aqueous solution, which reduced Fehling's solution actively on warming, was heated for 10 minutes at 70°, neutralised with barium carbonate, and filtered. The filtrate was evaporated under diminished pressure to 10 c.c., treated with bromine (0·8 c.c.) in the presence of excess barium carbonate for 2 days, and the excess of bromine removed by aeration; the solution now no longer reduced boiling Fehling's solution. Barium hydroxide solution (0·3N) was added until the solution was just alkaline to phenolphthalein in order to precipitate the barium oxalate and tartrate, and complete precipitation of the latter effected by addition of methyl alcohol (2 vols.). The insoluble barium salts were filtered off, washed with methyl alcohol to remove barium bromide, dried in a vacuum over phosphoric oxide, and boiled for 8 hours with 1% methyl-alcoholic hydrogen chloride (250 c.c.). The solution was cooled, neutralised with barium carbonate, filtered, and evaporated to dryness under diminished pressure, whereby the methyl oxalate was volatilised. The syrupy residue, after purification by extraction with ether to eliminate some inorganic impurity, readily crystallised upon nucleation with methyl dimethoxy *l*-threo-succinate (methyl dimethyl *d*-tartrate), and after recrystallisation from ether the methyl ester (0·56 g.) had m. p. and mixed m. p. 48°, $[\alpha]_D^{20°}$ +19° in water (*c*, 2·0) (Found: OMe, 34·6. Calc. for $C_6H_{10}O_6$: OMe, 34·8%).

Glucosaccharo-1 : 5-3 : 6-dilactone (IX).—Finely powdered glucosaccharo-3 : 6-lactone (m. p. 149°) (1 g.) contained in a test-tube was inserted in a Fischer dryer and heated in a vacuum at 100°. After 2—3 hours the lactone gradually melted and there was a slow evolution of bubbles from the colourless, stiff syrup. The heating was continued until no more bubbles were evolved, and while at this temperature the syrup crystallised spontaneously. When crystallisation was complete, the heating was stopped, and the product was crystallised from acetone–light petroleum. The glucosaccharo-1 : 5-3 : 6-dilactone was obtained as colourless needles, m. p. 133° (Found: C, 41·6; H, 3·9. Calc. for $C_6H_6O_6$: C, 41·4; H, 3·45%); $[\alpha]_D^{20°}$ +167° in water (*c*, 1·0) (initial value); +126° (2 hrs.); +113·5° (2½ hrs.) +87·5° (5 hrs.); +75° (7½ hrs.); +66° (10 hrs.); +53·5° (15 hrs.); +44·5° (21½ hrs.); +43·5° (90 hrs.) (constant for 10 hrs.). This dilactone reduces boiling Fehling's solution actively, and its freshly prepared aqueous solution is acid to litmus.

Evaporation in a vacuum at room temperature of an aqueous solution of the dilactone (25 mg.) after the rotation had reached the equilibrium value gave a colourless, thin syrup, and while containing some water this syrup was nucleated with a crystal of saccharo-3 : 6-lactone. The last traces of water were eliminated by evaporation in a vacuum over phosphoric oxide. The residue was triturated with acetone, and pure glucosaccharo-3 : 6-lactone, m. p. and mixed m. p. 149°, remained.

Glucosaccharo-1 : 4-3 : 6-dilactone (X).—Finely ground glucosaccharo-1 : 4-lactone monohydrate (1 g.) was heated for 2 hours at 60° in a vacuum. The m. p. (originally 98°) gradually rose until after 3 hours it was 115—125°. This product evidently contained some dilactone, because it reduced boiling Fehling's solution slightly and showed $[\alpha]_D^{18°}$ +60° in water (*c*, 1·5) (initial value), changing in 1 day to +38°; when a small portion of it was melted, it displayed immediately an increase in reducing activity towards boiling Fehling's solution. The product was then further heated at 100° in a vacuum; it gradually melted, and after 18 hours lactonisation appeared to be complete. The glucosaccharo-1 : 4-3 : 6-dilactone, which was a pale yellow glass, failed to crystallise. An aqueous solution of it reacted acid to Congo-red paper and showed $[\alpha]_D^{18°}$ +155° in water (*c*, 2·0) (initial value); +135° (1 hr.); +117·5° (2 hrs.); +102·5° (3 hrs.); +92·5° (4 hrs.); +83° (5 hrs.); +70° (7 hrs.); +65° (8 hrs.); +58° (10 hrs.); +54° (12 hrs.); +51° (14 hrs.); +47·5° (20 hrs.); +43·5° (32 hrs.); subsequently there was a gradual decrease in rotation to *ca.* $[\alpha]_D^{18°}$ +31·5° (7 days). The dilactone reduces Fehling's solution actively (Found: C, 41·5; H, 3·9. Calc. for $C_6H_6O_6$: C, 41·4; H, 3·5%).

Evaporation in a vacuum of an aqueous solution of this dilactone which had reached equilibrium gave a syrup which, whilst still containing a little water, readily crystallised upon nucleation with a specimen of glucosaccharo-3 : 6-lactone. Trituration with acetone followed by filtration gave glucosaccharo-3 : 6-lactone, m. p. and mixed m. p. 148°. Removal of the acetone from the mother-liquors gave a syrup which slowly crystallised on exposure to air. After trituration with ethyl acetate–acetone, these crystals of glucosaccharo-1 : 4-lactone monohydrate had m. p. 88°.

Treatment of Glucosaccharo-1 : 4-3 : 6-dilactone with Silver Oxide and Methyl Iodide.—The syrupy dilactone (0·54 g.), prepared as above, was dissolved in dry acetone (5 c.c.) and heated with methyl iodide (5 c.c.) and silver oxide (3—4 g.), the latter being added in small portions during the first 5 hours. After 8 hours the mixture was extracted with hot acetone; the solution was filtered and evaporated to dryness under diminished pressure, and the syrupy product given 3 more treatments with silver oxide and methyl iodide (no acetone used). After this procedure the product crystallised spontaneously. Trituration with ethyl alcohol–ether to remove adhering syrup, followed by crystallisation of the product from ethyl alcohol, gave 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester, m. p. and mixed m. p. 89°, $[\alpha]_D^{18°}$ +92° in water (*c*, 1·4) (Found: C, 50·2; H, 5·65; OMe, 42·7. Calc. for $C_9H_{12}O_6$: C, 50·0; H, 5·6; OMe, 43·0%). Distillation of the syrup obtained from the mother-liquors gave a colourless liquid (0·3 g.), b. p. (bath temp.) 148—168°/0·04 mm., $n_D^{19°}$ 1·4744, from which a further 0·12 g. of 2 : 5-dimethyl glucosaccharo-3 : 6-lactone 1-methyl ester was separated. Treatment of the syrup obtained (0·18 g.) from the mother-liquors, after the removal of crystals (0·12 g.), with methyl-alcoholic ammonia gave a diamide (10 mg.), m. p. 202°, $[\alpha]_D^{20°}$ +19° in water (*c*, 2·0) (after recrystallisation from ethyl alcohol) (Found: C, 44·4; H, 6·9; N, 11·8; OMe, 37·5. Calc. for $C_9H_{18}O_6N_2$: C, 43·2; H, 7·2; N, 11·2; OMe, 37·2%). This amide (as yet unidentified) gave no depression of the m. p. when mixed with an amide obtained in small yield from a corresponding fraction of methylated glucosaccharo-1 : 5-3 : 6-dilactone.

A. E. Hills Laboratories,
The University, Edgbaston, Birmingham, 15.

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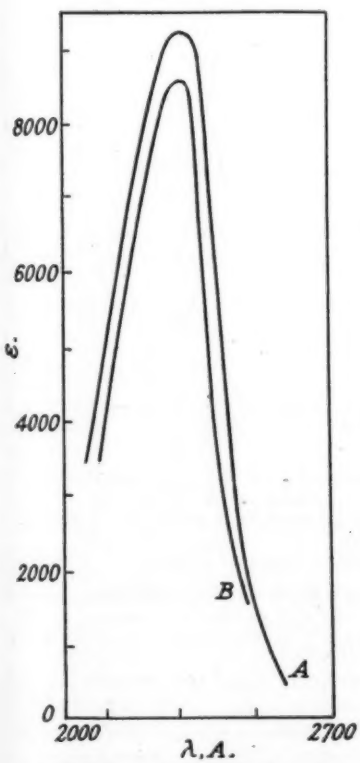
174. *Lactones of Glucosaccharic Acid. Part IV. The Enol of 5-Keto-4-deoxyglucosaccharo-3 : 6-lactone, an Analogue of Ascorbic Acid.*

By (Miss) D. Heslop and F. Smith.

Glucosaccharo-1 : 5-3 : 6-dilactone (V), glucosaccharo-1 : 4-3 : 6-dilactone (IV), glucosaccharo-1 : 4-lactone 6-methyl ester (II; R = Me), and glucosaccharo-3 : 6-lactone 1-methyl ester (III; R = Me) all reduce Fehling's solution. The peculiar reducing activity of these four substances is shown to be due to isomerisation brought about by alkaline reagents whereby there is produced from each of them the highly reducing enol of 5-keto-4-deoxyglucosaccharo-3 : 6-lactone (VIII; R = R′ = H), the structure of which is established. Ozonisation of this lactone gave oxalic acid and *l*-threouronic acid (IX), the latter being identified by its oxidation to dihydroxy-*l*-threosuccinic acid (*d*-tartaric acid) (IX; but CO_2H for CHO). Methylation of (VIII; R = R′ = H) with diazomethane yielded the corresponding 5-methyl ether of the ester lactone (VIII; R = Me, R′ = H), and this was converted by the agency of silver oxide and methyl iodide into the characteristic crystalline 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester (VIII; R = R′ = Me).

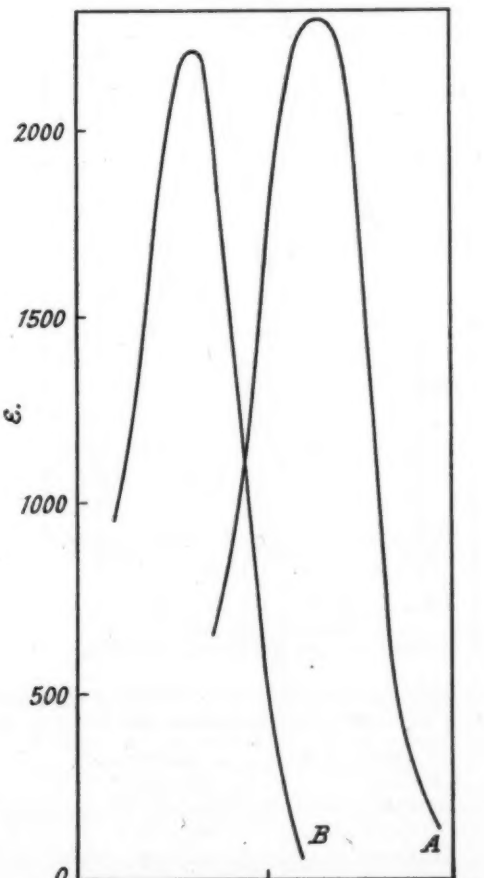
Lactonisation of saccharic acid by concentration of an aqueous solution yielded two monolactones, glucosaccharo-1 : 4- (II; R = H) and -3 : 6-lactone (III; R = H), the latter being obtained in much the greater

Fig. 1.



A. *5-Methyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester in water* (4 *mg.* %).
B. *2 : 5-Dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester in water* (4 *mg.* %).

Fig. 2.

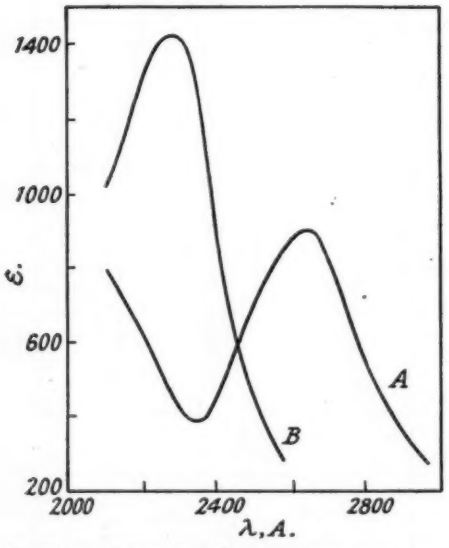


A. *Glucosaccharo-1 : 5-3 : 6-dilactone in ethyl alcohol, to which was added aqueous sodium hydroxide* (10 *mg.* %).
B. *Solution used for* A *acidified* (10 *mg.* %).

proportion. By means of diazomethane these two lactones were converted into the corresponding ester lactones (II; R = Me) and (III; R = Me) and by heating in a vacuum at 100° the two monolactones (II; R = H) and (III; R = H) afforded glucosaccharo-1 : 5-3 : 6-dilactone (V) and glucosaccharo-1 : 4-3 : 6-dilactone (IV) respectively (Smith, this vol., p. 510). It was pointed out that the four substances (II; R = Me), (III; R = Me), (IV), and (V) had the peculiar property of reducing Fehling's solution, a phenomenon also displayed

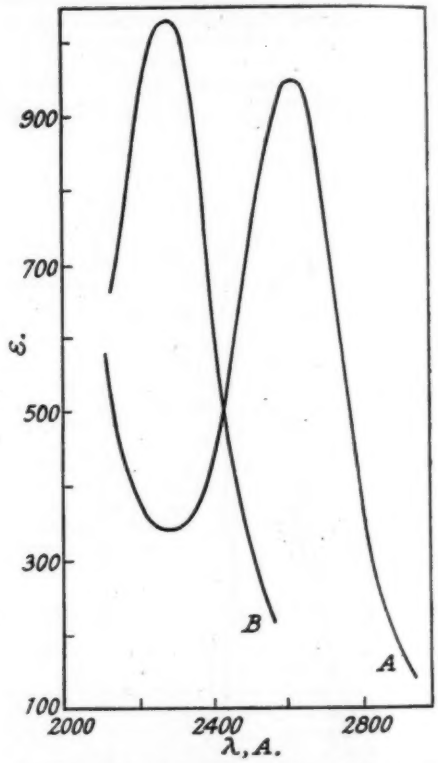
by mannosaccharo-1 : 4-3 : 6-dilactone (VI) (Kiliani, *Ber.*, 1887, **20**, 2710; Fischer, *Ber.*, 1891, **24**, 539). It was demonstrated by the present authors that the reducing activity of the latter was due to the production by alkaline reagents of an unsaturated isomer of the dilactone which proved to be the enol of 5-keto-4-deoxy-mannosaccharo-3 : 6-lactone (VII) (this vol., p. 224). The work herein described proves that a compound analogous to (VII) is responsible for the reducing activity shown by the two glucosaccharodilactones (IV) and (V), and the two ester lactones (II; R = Me) and (III; R = Me). The evidence which led to this conclusion is as follows: Methylation of all these four substances gave rise to 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester (VIII; R = R′ = Me), an analogue of ascorbic acid displaying a selective absorption band at λ 2290 A. (Fig. 1). When these four lactones were separately treated with alkaline reagents, isomerisation took

FIG. 3.



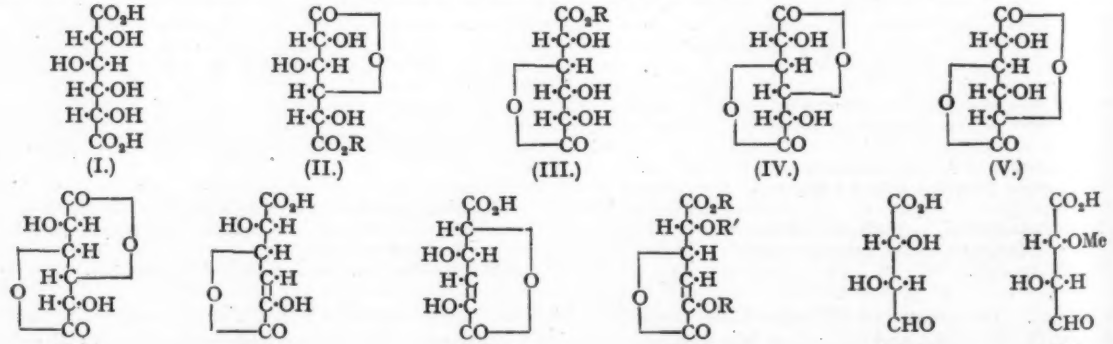
A. *Glucosaccharo-1 : 4-3 : 6-dilactone in aqueous alkali* (19 *mg.* %).
B. *Solution used for* A *acidified* (19 *mg.* %).

FIG. 4.



A. *Glucosaccharo-3 : 6-lactone 1-methyl ester in aqueous alkali* (40 *mg.* %).
B. *Solution used for* A *acidified* (26 *mg.* %).

place with the formation of a substance which exhibits in alkaline solution a band at λ 2630 A. Acidification of each of these solutions caused the band to move to λ 2290 A. (Figs. 2, 3, 4, 5), the position of the band

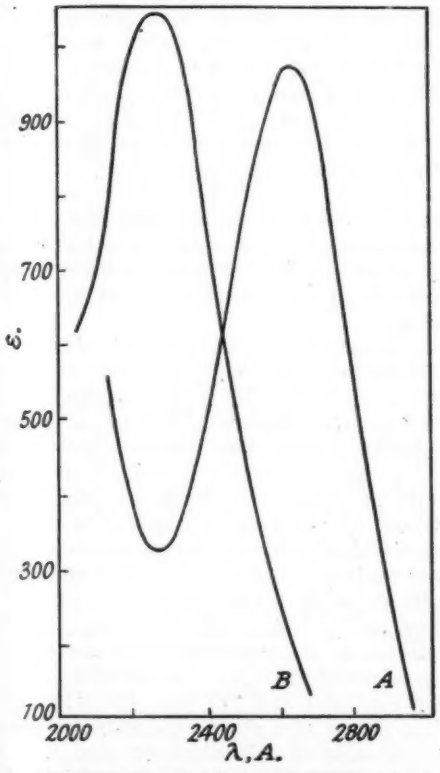


shown by (VIII; R = R′ = Me). Such acidified solutions showed reducing activity to a marked degree; *e.g.*, they reacted immediately with chlorine or bromine, rapidly decolorised potassium permanganate, and

reduced Fehling's solution actively. The substance formed from these four compounds was thought to be the same in each case and closely related to 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester (VIII; R = R′ = Me), and indeed it was suggested that the reactive reducing substance was the unmethylated form of this (Smith, this vol., p. 510).

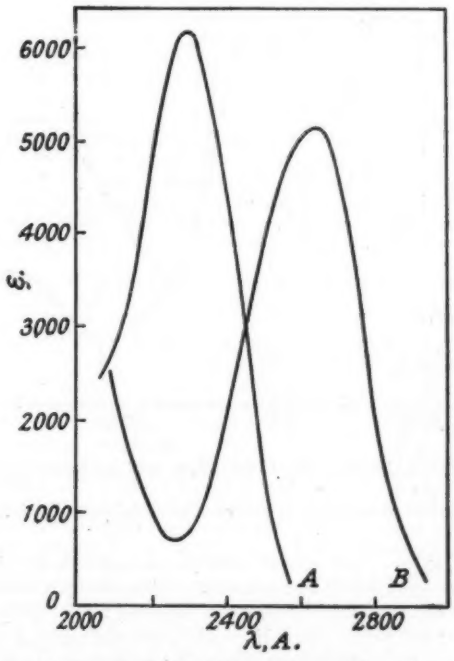
When glucosaccharo-1 : 5-3 : 6-dilactone (V) was treated with methyl-alcoholic sodium methoxide, followed by methyl-alcoholic hydrogen chloride, there was formed a syrup which displayed all the reducing properties referred to above and had an absorption band at λ 2290 A. moving to λ 2630 A. on addition of sodium hydroxide. Methylation of this syrup with silver oxide and methyl iodide gave in good yield 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester (VIII; R = R′ = Me); these facts suggested, but did not prove, that the unmethylated form of (VIII; R = R′ = Me) was present in the syrup before methylation. Ozonisation of this syrup in glacial acetic acid gave oxalic acid and an aldehydic acid (IX), which upon oxidation with bromine gave rise to dihydroxy-*l*-threosuccinic acid (IX; but CO_2H for CHO). There was thus good evidence for the existence of a compound, in the syrup examined, possessing the reducing system ·C(OH):CH·

FIG. 5.



A. *Glucosaccharo-1 : 4-lactone 6-methyl ester in aqueous alkali* (41 *mg.* %).
B. *Solution used for* A *acidified* (27 *mg.* %).

FIG. 6.



A. *Enol of 5-keto-4-deoxyglucosaccharo-3 : 6-lactone in water* (5 *mg.* %).
B. *Enol of 5-keto-4-deoxyglucosaccharo-3 : 6-lactone in aqueous alkali* (5 *mg.* %).

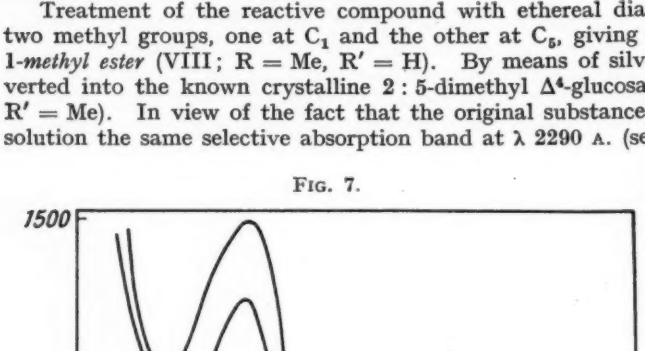
and one, probably the same substance, which affords 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester (VIII; R = R′ = Me) upon methylation.

Careful control of the conditions for the isomerisation of the dilactone (V) by the agency of sodium methoxide resulted in the isolation of the reactive substance itself in the crystalline form. By a similar procedure the same crystalline substance was obtained from the second dilactone (IV) and the two ester lactones (II; R = Me) and (III; R = Me) (see Figs. 2, 3, 4, 5, 6). The crystalline, reactive substance to which the structure (VIII; R = R′ = H) has been given was acid, and displayed mutarotation in aqueous solution; it showed a strong selective absorption band at λ 2290 A., moving to λ 2630 A. upon addition of sodium hydroxide (Fig. 6), and it reacted in the cold with 2 equivs. of sodium hydroxide, thus indicating the presence of two acid groups. In aqueous solution (VIII; R = R′ = H), like the enol of 5-keto-4-deoxymannosaccharolactone (VII) (Heslop and Smith, *loc. cit.*), reacted with four atomic proportions of chlorine, and in alkaline solution with six atomic proportions of iodine. When subjected to ozonolysis in glacial acetic acid (VIII; R = R′ = H) gave oxalic acid and the highly reducing, aldehydic acid, threuronic acid (IX), characterised by its oxidation with bromine to dihydroxy-*l*-threosuccinic acid (dextro-tartaric acid) (IX; but CO_2H for CHO). No glyoxylic acid was formed. These facts located the position of the double bond between C_4 and C_5 and proved that the system

·CH:C(OH)·CO was present in the crystalline reducing enolic compound (VIII; R = R′ = H). The isolation of the tartaric acid also proved that the stereochemical arrangement of H and OH groups at C_2 and C_3 was the same as that obtaining in this acid. Although these observations lent strong support to the view that the reactive crystalline substance had structure (VIII; R = R′ = H), they did not enable a choice to be made between this and the other possible formula (VIII*a*), for both these structures explained the results of ozonolysis. The following series of transformations, however, proved conclusively that the furone structure (VIII; R = R′ = H) was correct.

Treatment of the reactive compound with ethereal diazomethane effected the smooth introduction of two methyl groups, one at C_1 and the other at C_5, giving crystalline *5-methyl* Δ^4*-glucosaccharo-3 : 6-lactone 1-methyl ester* (VIII; R = Me, R′ = H). By means of silver oxide and methyl iodide the latter was converted into the known crystalline 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester (VIII; R = R′ = Me). In view of the fact that the original substance and these two derivatives all show in aqueous solution the same selective absorption band at λ 2290 A. (see Figs. 6 and 1), it was evident that the transformation of (VIII; R = R′ = H) into (VIII; R = R′ = Me) *via* (VIII; R = Me, R′ = H) had been performed without any change in structure. It follows, therefore, that the isolation of the known 2 : 5-dimethyl Δ^4-glucosaccharo-3 : 6-lactone 1-methyl ester (VIII; R = R′ = Me) proved that a 3 : 6- and not a 2 : 6-lactone ring was present in all three substances. Hence, the structure (VIII; R = R′ = H) was confirmed for the reducing compound derived as above, and this *enol* of *5-keto-4-deoxyglucosaccharo-3 : 6-lactone* is the substance responsible for the curious reducing activity displayed by the substances from which it is derived.

FIG. 7.



A. *Ethyl glucosaccharate in dilute sodium hydroxide* (370 *mg.*/100 *c.c.*).
B. *Solution used for* B *acidified with dilute sulphuric acid.*

It is noteworthy that saccharic acid (I) and glucosaccharo-1 : 4- (II; R = H) and -3 : 6-lactones (III; R = H) do not reduce Fehling's solution. This curious property of reducing Fehling's solution which is due to the isomerisation to the enol (VIII; R = R′ = H) brought about by the agency of alkaline reagents is shown by those four derivatives referred to above, in each of which both carboxyl groups are esterified either as internal esters, *i.e.*, (IV) and (V), or esterified partly in this manner and partly with methyl alcohol, *i.e.*, (II; R = Me) and (III; R = Me). The isomerisation of these substances under the influence of alkaline reagents is not therefore dependent upon the presence of two interlocking rings (Rehorst, *Ber.*, 1938, **71**, 923). In addition, although it is not surprising that saccharo-1 : 4-3 : 6- and -1 : 5-3 : 6-dilactones, (IV) and (V), and the 3 : 6-lactone 1-methyl ester (III; R = Me), all containing the 3 : 6-lactone ring, should give rise to the reducing enol of 5-keto-4-deoxyglucosaccharo-3 : 6-lactone, yet it is remarkable that this enol is obtained also from the 1 : 4-lactone ester (II; R = Me), for this transformation must involve the scission of the 1 : 4-ring and the introduction of the 3 : 6-lactone ring.

In this connection it should be noted that ethyl glucosaccharate, which has both carboxyl groups esterified, also shows reducing activity towards Fehling's solution, though to a less extent than the four substances in question, but whether the same enol (VIII; R = R′ = H) is produced from this ester with alkaline reagents is not yet known. The reaction is clearly not so simple in this case because the absorption band shown by ethyl glucosaccharate in alkaline solution (Fig. 7) is different from that shown by the other four substances in alkaline solution and, furthermore, acidification of its alkaline solution does not result in the appearance of the band at λ 2290 A. (Fig. 7).

EXPERIMENTAL.

Treatment of Saccharo-1 : 5-3 : 6-dilactone (V) *with Sodium Methoxide.*—The dilactone (5 g.) was dissolved in ethyl alcohol (25 c.c.) and treated with 3 equivs. of sodium methoxide (73 c.c.; 1·18N) for 5 minutes. To 5 c.c. of the solution was added ethyl alcohol (30 c.c.) with stirring, and the sodium derivative thus precipitated was centrifuged off, washed with ethyl alcohol, ether, and dried in a vacuum (Found: Na, 17%). This sodium derivative had $[\alpha]_D^{20°}$ + 10° in 0·2N-sulphuric acid (*c*, 1·5); I.V., 145. It reduced Fehling's solution actively.

To the main bulk of the solution was added methyl-alcoholic hydrogen chloride (57·6 c.c.; 1·44N). The solution was then evaporated to dryness in a vacuum, extracted with ethyl alcohol, and filtered. Removal of the solvent gave a pale yellow syrup which reacted acid to Congo-red paper and reduced Fehling's solution actively on warming. This product immediately decolorised bromine water and potassium permanganate. It showed selective absorption with the head of the band at λ 2290 A. (ε, ca. 3500) (*c*, 5 mg. % in water).

Ozonisation. A solution of the syrupy reducing product in glacial acetic acid (40 c.c.) was subjected to the action of a steady stream of ozonised oxygen at room temperature. After two hours, two drops of the solution were removed, diluted to 1 c.c., and boiled for one minute. This solution gave a positive oxalate test, and reduced Fehling's solution in the cold after 2—3 minutes. Little or no change in rotation was observed during the ozonolysis, which was continued for 9 hours. At this stage oxalic acid could be detected readily, and the solution reduced Fehling's solution in the cold. The main bulk of the solution was diluted with water (50 c.c.) and evaporated under diminished pressure to remove acetic acid, a process facilitated by addition and distillation of further small amounts of water. When freed from acetic acid and water, the product (6·3 g.) reacted acid to Congo-red paper and reduced Fehling's solution in the cold.

A portion of this syrup (5·2 mg.) in water (1 c.c.) was made just alkaline by the addition of 0·1N-sodium hydroxide, and then acidified with dilute acetic acid. Two drops of calcium chloride were added, the mixture warmed, and the precipitated calcium oxalate centrifuged and washed twice with distilled water on the centrifuge. The precipitate was dissolved in 0·1N-sulphuric acid, the solution heated to 70°, and titrated with 0·02N-potassium permanganate (1 c.c. required). This corresponds to 1·1 g. of oxalic acid in the total weight of syrup (6·3 g.).

In alkaline solution the syrup (18·6 mg.) reacted with 5·6 c.c. of 0·02N-iodine, corresponding to the presence of 2·5 g. of threuronic acid in the 6·3 g. of syrup obtained after ozonisation.

Oxidation with bromine. The syrup (6·2 g.) obtained as above was dissolved in water (20 c.c.) and treated with bromine (1·5 c.c.). After standing overnight, a portion of the solution, when freed from excess of bromine by aeration, still reduced Fehling's solution. Barium carbonate (5 g.) and bromine (1 c.c.) were added, and the oxidation allowed to proceed for a further 24 hours; it was then complete, and the excess of the bromine was removed by aeration. The white precipitate (A) formed during the oxidation was filtered off, washed with water, and dried (3·8 g.); this was barium oxalate and corresponded to 1·15 g. of oxalic acid. The filtrate, which was acid and showed $[\alpha]_D^{20°}$ +25°, was neutralised (litmus) by addition of 0·3N-barium hydroxide, whereby there was obtained a precipitate (B) (1·07 g.), which was filtered off, washed with water, alcohol, ether, and dried in a vacuum. To the neutral filtrate (after the separation of B) was added 0·3N-barium hydroxide until the liquid reacted weakly alkaline to phenolphthalein; this afforded precipitate (C) (1·7 g.) which showed a positive test for tartrate when heated with concentrated sulphuric acid and β-naphthol. After removal of (C), addition of 0·3N-barium hydroxide to the liquid until there was no further precipitation, followed by ethyl alcohol (equal in volume to the aqueous solution), gave a precipitate (D) (4·7 g.), which also showed a positive tartrate test. The precipitates (C) and (D) were washed with alcohol, ether, and dried in a vacuum.

Examination of precipitates (B), (C), and (D). These fractions were combined (7 g.) and boiled for 8 hours with 2·5% methyl-alcoholic hydrogen chloride (200 c.c.). The solution was cooled, neutralised with silver carbonate, and an equal volume of ether added to precipitate the dissolved barium chloride, which was filtered off and washed with ether. Removal of the solvent from the combined filtrate and washings gave a liquid which was purified by distillation (1·8 g.), b. p. 180° (bath temp.)/20 mm. The distillate crystallised spontaneously, and after trituration with ether–alcohol the methyl dihydroxythreosuccinate (methyl *d*-tartrate) had m. p. and mixed m. p. 49°, $[\alpha]_D^{18°}$ +19° in water (*c*, 2·4) (Found: OMe, 35·4. Calc. for $C_6H_{10}O_6$: OMe, 34·8%).

Treatment of this ester with methyl-alcoholic ammonia for 2 days at − 5° gave dihydroxythreosuccinamide, which crystallised upon removal of the solvent in a vacuum; m. p. 205—206° (decomp.), $[\alpha]_D^{18°}$ +116·5° in water (*c*, 1·2) (after three crystallisations from aqueous alcohol).

Isolation of 2 : 5-*Dimethyl* Δ^4-*Glucosaccharo*-3 : 6-*lactone* 1-*Methyl Ester* (VIII; R = R′ = Me).—In another experiment the glucosaccharo-1 : 5-3 : 6-dilactone (V) (0·5 g.) was dissolved in ethyl alcohol (10 c.c.) and treated with sodium methoxide (8 c.c.; 1·2N) for 5 minutes at room temperature, followed by methyl-alcoholic hydrogen chloride (4 c.c.; 2·4N). The solution was evaporated to dryness and extracted with ethyl alcohol. Removal of the ethyl alcohol gave a pale yellow, acid syrup, which was subjected to two methylations with silver oxide and methyl iodide, the first requiring a little methyl alcohol to aid complete solution of the product. The methyl ester (VIII; R = R′ = Me) was isolated by means of acetone and dissolved in a small volume of hot ether; on cooling 0·33 g. separated, m. p. and mixed m. p. 88°.

Formation of the Enol of 5-*Keto*-4-*deoxyglucosaccharo*-3 : 6-*lactone* (VIII; R = R′ = H) *by Alkaline Isomerisation.*—(a) *Of glucosaccharo*-1 : 5-3 : 6-*dilactone* (V). To a solution of the dilactone (m. p. 133°, $[\alpha]_D^{18°}$ +166° initial value in water) (1 g.) in dry methyl alcohol (10 c.c.) were added 3 equivs. of methyl-alcoholic sodium methoxide (15 c.c.; 1·2N). After 5 minutes the solution was treated with 3 equivs. of methyl-alcoholic hydrogen chloride (18 c.c.; N), then evaporated to dryness under diminished pressure at 40°, and the residue extracted with ether. Removal of the ether under slightly reduced pressure gave a pale yellow syrup which crystallised slowly on keeping. Trituration with ether–acetone to remove adhering syrup, followed by recrystallisation from ether–acetone, gave the *enol* of 5-*keto*-4-*deoxyglucosaccharo*-3 : 6-*lactone* (72 mg.), m. p. 159°, $[\alpha]_D^{18°}$ +39° in water (*c*, 1·5) (Found: C, 40·5; H, 3·9. $C_6H_8O_6$ requires C, 41·3; H, 3·5%). *Absorption.* A solution of glucosaccharo-1 : 5-3 : 6-dilactone in 50% aqueous ethyl alcohol showed on addition of an excess of N-sodium hydroxide a band at λ 2630 A. (ε, 2500 approx.; *c*, 10 mg. %), and on acidification the band moved to λ 2290 A. (ε, 2200 approx.; *c*, 10 mg. %) (see Fig. 2).

(b) *Of glucosaccharo*-1 : 4-3 : 6-*dilactone* (IV). Glucosaccharo-1 : 4-lactone monohydrate (1 g.) was converted into this lactone by 15 hours' heating in a vacuum at 100° (see Heslop and Smith, *loc. cit.*), and a solution of this dilactone (0·78 g.) in dry methyl alcohol (10 c.c.) was treated with 3 equivs. of sodium methoxide for 4 minutes. Addition of 3 equivs. of hydrogen chloride in methyl alcohol, followed by removal of solvent under reduced pressure, gave a residue from which the above enol was extracted with ether. Evaporation of ether gave a syrup, which crystallised on keeping. Trituration with ethyl alcohol gave the pure enol (0·27 g.), m. p. 159°, $[\alpha]_D^{20°}$ +38° in water (*c*, 2·4). *Absorption.* In aqueous alkaline solution the dilactone (VI) showed a band at λ 2650 A. (ε, 900 approx.; *c*, 19 mg. %), moving on acidification to λ 2290 A. (ε, 1400 approx.; *c*, 19 mg. %) (see Fig. 3). In alcoholic solution the isomerisation of the dilactone to the enol proceeds to a greater extent; *e.g.*, a solution of the dilactone in methyl alcohol after treatment with sodium methoxide shows a band at λ 2630 A. (ε, 4500 approx.; *c*, 5 mg. %).

(c) *Of glucosaccharo*-1 : 4-*lactone* 6-*methyl ester* (II; R = Me). This ester (0·8 g.), treated as described above with 3 equivs. of sodium methoxide for 5 minutes, followed by methyl-alcoholic hydrogen chloride, yielded the same enol (VIII; R = R′ = H) (0·15 g.), m. p. 159°, $[\alpha]_D^{20°}$ +39·5° in water (*c*, 2·0). *Absorption.* To 1·64 mg. of the crystalline ester (II; R = Me) was added 1 drop of 5N-sodium hydroxide, and the volume made up to 4 c.c. This solution showed a band at λ 2650 A. (ε, 1000 approx.; *c*, 41 mg. %), moving to λ 2290 A. upon acidification with 5N-sulphuric acid (see Fig. 5).

(d) *Of glucosaccharo*-3 : 6-*lactone* 1-*methyl ester* (III; R = Me). This ester (1·6 g.), made by the method previously given (Smith, *loc. cit.*), was dissolved in dry methyl alcohol (10 c.c.) and treated with sodium methoxide for 4 minutes, followed by methyl-alcoholic hydrogen chloride in the manner described above. After isolation by extraction with ether–ethyl alcohol, the enol had m. p. 159°, $[\alpha]_D^{19°}$ +39° in water (*c*, 2·9). *Absorption.* Aqueous alkaline solutions of glucosaccharo-3 : 6-lactone 1-methyl ester show a band at λ 2630 A. (ε, 900 approx.; *c*, 60 mg. %), moving upon acidification to λ 2290 A. (ε, 1000 approx.; *c*, 26 mg. %).

The enol of 5-keto-4-deoxyglucosaccharo-3 : 6-lactone reacted acid to Congo-red; it reduced Fehling's solution actively on warming, decolorised potassium permanganate solution immediately, and also decolorised bromine water. Unlike ascorbic acid, the enol does not reduce silver nitrate solution.

In aqueous solution the enol showed a band at λ 2290 A. (ε, 6000; *c*, 5 mg. %), moving on addition of sodium hydroxide to λ 2650 A. (ε, 5000; *c*, 5 mg. %) (Fig. 6). It reacted immediately with 2 equivs. of sodium hydroxide at room temperature (9·81 mg. required 11·02 c.c. of 0·01N-solution, corresponding to equiv., 89. Calc. for $C_6H_8O_6$: equiv., 87). The enol reacted with 6·2 atomic proportions of iodine in alkaline solution (5·85 mg. required 20·8 c.c. of 0·01N-iodine), and in aqueous solution it combined with 4 atomic proportions of chlorine (9·46 mg. required 10·84 c.c. of 0·02N-chlorine water. Calc. : 10·87 c.c.).

Ozonisation of the Enol of 5-Keto-4-deoxyglucosaccharolactone.—A solution of this compound (0·46 g.) in glacial acetic acid (30 c.c.) was subjected to the action of a stream of ozonised oxygen during 9 hours. The solution showed $[\alpha]_D^{18°}$ +33° (initial value); +20° (after 1 hr.); +8° (2 hrs.); +5° (3 hrs.); +3° (4 hrs.); ±0° (5 hrs.; constant value). After addition of water, followed by distillation under reduced pressure to remove acetic acid and water, there was obtained a syrupy product, which reacted acid to Congo-red and reduced Fehling's solution actively; it contained oxalic acid (calcium chloride test). The aqueous acetic acid distillate gave a negative test for glyoxylic acid (tested with albumin and concentrated sulphuric acid).

Oxidation with bromine. A solution of the syrupy product from the ozonisation in water (10 c.c.) was treated with bromine (0·2 c.c.) at room temperature for 14 hours in the presence of a small amount of barium carbonate. The excess of bromine was removed by aeration, and the aqueous acid solution, which did not now reduce Fehling's solution, was neutralised by careful addition of barium hydroxide. The precipitate of barium salts was dried.

Esterification. The dry barium salts (0·42 g.) were boiled for 8 hours with 2% methyl-alcoholic hydrogen chloride (100 c.c.), the solution cooled, neutralised with silver carbonate, filtered, and concentrated in a vacuum. Purification of the resulting liquid by extraction with acetone, followed by removal of the solvent, gave a liquid (0·15 g.), b. p. (bath temp.) 130°/0·04 mm., $n_D^{20°}$ 1·4394, which crystallised spontaneously. After recrystallisation from ether the methyl dihydroxy-*l*-threosuccinate (methyl *d*-tartrate) had m. p. and mixed m. p. 48°, $[\alpha]_D^{19°}$ +19° in water (*c*, 2·5). Treatment of this methyl ester with methyl-alcoholic ammonia for 15 hours gave the corresponding diamide (*d*-tartramide), m. p. 202°, $[\alpha]_D^{18°}$ +105° in water (*c*, 4·0) (Found : C, 32·6; H, 5·55; N, 18·7. Calc. for $C_4H_8O_4N_2$: C, 32·4; H, 5·4; N, 18·9%).

Treatment of the Enol of 5-Keto-4-deoxyglucosaccharo-3 : 6-lactone with Chlorine.—The crystalline enol (0·3 g.), dissolved in water (3 c.c.), was treated for 15 minutes with 0·02N-chlorine water (50 c.c.). The excess of chlorine was removed by aeration, and the solution neutralised with barium carbonate, filtered, and evaporated to dryness in a vacuum. The residue, consisting of the barium salt of an organic acid, was boiled for 8 hours with 2% methyl-alcoholic hydrogen chloride (50 c.c.). The solution was cooled and neutralised (Congo-red) with barium carbonate. After filtration and evaporation under diminished pressure, there was obtained a syrup (0·25 g.) which still reacted acid to Congo-red. This was esterified by treatment with a slight excess of a solution of ethereal diazomethane at 0°. Removal of solvent gave a neutral liquid (0·11 g.), b. p. (bath temp.) 140—150°/0·03 mm., $[\alpha]_D^{15°}$ +42° in water (*c*, 0·8). This product reduced Fehling's solution on boiling (Found : OMe, 28·0. $C_9H_{14}O_7Cl_2$ requires OMe, 30·5%).

Treatment of this syrup (90 mg.) with methyl-alcoholic ammonia for 3 days at − 5° gave a crystalline *amide* believed to be the (C_1) monoamide of methyl 4 : 5-dichloro-2 : 3-dihydroxy-5-methoxyadipate, m. p. 189° (after recrystallisation from acetone) (Found : C, 33·6; H, 4·0; N, 5·4; OMe, 20·6. $C_8H_{13}O_6NCl_2$ requires C, 33·1; H, 4·5; N, 4·8; OMe, 21·4%). This compound is analogous to the one prepared from the enol of 5-keto-4-deoxymannosaccharo-3 : 6-lactone (Heslop and Smith, *loc. cit.*).

5-Methyl Δ^4*-Glucosaccharo-3 : 6-lactone 1-Methyl Ester* (VIII; R = Me, R′ = H).—A solution of the enol (0·1 g.) in dry methyl alcohol (5 c.c.) was treated with a slight excess of ethereal diazomethane at 0°, as indicated by a yellow colour in the solution. Removal of the solvent after 5 minutes gave crystalline *5-methyl* Δ^4*-glucosaccharo-3 : 6-lactone 1-methyl ester*, m. p. 142°, $[\alpha]_D^{18°}$ +91° in water (*c*, 1·5) (after recrystallisation from ethyl alcohol) (Found : C, 47·8; H, 5·15; OMe, 30·3. $C_8H_{10}O_6$ requires C, 47·5; H, 5·0; OMe, 30·7%). An aqueous solution of this compound showed a band at λ 2290 A. (ε, 9000 approx.; *c*, 4 mg. %) (Fig. 1). On addition of sodium hydroxide this band disappeared. Reacidification with dilute sulphuric acid apparently regenerated the original unsaturated furone structure, for the solution showed a band at λ 2290 A. (ε, 1500 approx.).

This enol was shown to contain one ester methoxyl group as follows. The compound (15·64 mg.) was heated with 0·3N-barium hydroxide (3 c.c.) at 50° for 1 hour. The solution was neutralised (phenolphthalein) by shaking it gently while a stream of carbon dioxide was passed over the surface, then evaporated to dryness under diminished pressure at 50° in a current of dry air. All these operations were carried out in a Zeisel apparatus. A methoxyl estimation on the residue gave OMe, 15·35 (Calc. for loss of one OMe from $C_8H_{10}O_6$: OMe, 15·35%).

2 : *5-Dimethyl* Δ^4*-Glucosaccharo-3 : 6-lactone 1-Methyl Ester* (VIII; R = R′ = Me).—The foregoing 5-methyl ether (VIII; R = Me, R′ = H) (40 mg.) was given one methylation with silver oxide (1 g.) and methyl iodide (2 c.c.) during 8 hours. Extraction of the product with ethyl alcohol, followed by removal of the solvent, gave the crystalline compound (VIII; R = R′ = Me), m. p. and mixed m. p. 87°, $[\alpha]_D^{17°}$ +92° in water (*c*, 1·1) (after recrystallisation from ethyl alcohol–ether) (Found : C, 50·15; H, 5·6; OMe, 42·0. Calc. for $C_9H_{12}O_6$: C, 50·0; H, 5·6; OMe, 43·1%). An aqueous solution of this substance showed a band at λ 2290 A. (ε, 8500 approx.; *c*, 4 mg. %) (Fig. 1).

Treatment of Ethyl Glucosaccharate with Sodium Hydroxide.—A solution of ethyl glucosaccharate (11·1 mg.) in water (0·2 c.c.) was treated with 1 drop of 5N-sodium hydroxide, the solution brought to the boil, cooled, and diluted to 3 c.c., it then showed bands at λ 2660 A. (ε, 1500 approx.) and at λ 3280 A. (ε, 1000 approx.; *c*, 360 mg. %). Acidification of the alkaline solution caused no change in the position of the bands, but the intensity was reduced to approximately ε, 1300 and ε, 600 for the respective bands (*c*, 360 mg. %) (see Fig. 7).

THE A. E. HILLS LABORATORIES,
THE UNIVERSITY, EDGBASTON, BIRMINGHAM.

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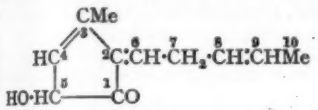
175. *The Structure of Pyrethrolone and Related Compounds. Part III.*

By T. F. WEST.

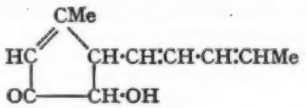
On hydrogenation the two methyl ethers derived from pyrethrolone (West, this vol., p. 239) were converted into the corresponding *tetrahydro*-compounds (cf. LaForge and Haller, *J. Amer. Chem. Soc.*, 1936, **58**, 1779). Attempts were made to remove one of the double bonds in the side chain in order to throw light upon the most probable position of the remaining double bond in relation to the unsaturation in the nucleus. *Dihydro-*

derivatives were obtained from both the *d*- and the *i*-pyrethrolone methyl ether by treatment with hydrogen bromide, followed by zinc reduction. Although the light absorption data for these compounds did not permit differentiation between the formulæ advanced for pyrethrolone during the past few years (Gillam and West, J., 1942, 671; 1944, 49; LaForge and Acree, *J. Org. Chem.*, 1942, **7**, 418; LaForge and Barthel, *ibid.*, 1944, **9**, 242; West, this vol., pp. 51, 239), they indicated that the two pairs of dihydro- and tetrahydro-derivatives contained similar chromophoric systems and with other analytical data it was possible to infer that in the dihydro-compounds it was the double bond nearest the nucleus which had been eliminated. The terminal methyl values for the two pyrethrolone methyl ethers and their derivatives appeared to lend support to the conclusion of LaForge and Barthel (*loc. cit.*) that pyrethrolone may not be a homogeneous compound.

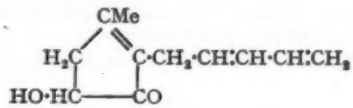
In Part II (this vol., p. 239) the relationship between the dextrorotatory methyl ether prepared from pyrethrolone and methyl sulphate and the optically inactive ether obtained from pyrethrolone semicarbazone with methyl-alcoholic sulphuric acid was examined. Arising mainly out of a study of the behaviour of these ethers towards dienophiles in the Diels–Alder reaction, a tentative structure (I) was suggested for pyrethrolone because of the chemical difficulties raised by the structures (II) and (III) which were suggested as possibilities by Gillam and West (J., 1942, 671) in an attempt to accommodate the light absorption data.



(I.)



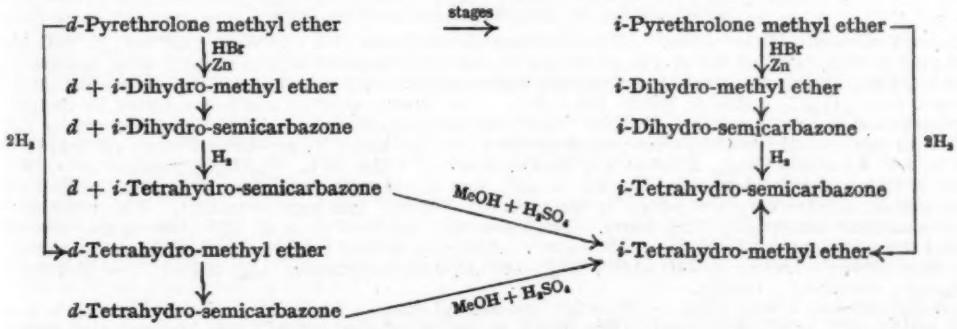
(II.)



(III.)

In order to test the correctness or otherwise of these postulated formulæ attempts have been made to eliminate one of the double bonds in the side chain. The methyl ethers of pyrethrolone were utilised in these experiments because of the tendency for migration of the double bonds in pyrethrolone itself—due no doubt to the juxtaposition of the >CO and >CH·OH groups in the *cyclo*pentenolone ring (Gillam and West, *loc. cit.*; West, *loc. cit.*). For comparison as an end product *d*-pyrethrolone methyl ether was hydrogenated to d-*tetrahydropyrethrolone methyl ether* and the *i*-ether, under similar conditions, gave the i-*tetrahydropyrethrolone methyl ether*. d-*Tetrahydropyrethrolone methyl ether semicarbazone* was converted into the inactive tetrahydro-ether by refluxing with methyl-alcoholic sulphuric acid.

LaForge and Haller (*J. Org. Chem.*, 1938, **2**, 546) found that on treatment with aluminium amalgam pyrethrolone was converted into its deoxy-derivative, pyrethrone, but when treated under the same conditions both the *d*- and the *i*-pyrethrolone methyl ether were recovered substantially unchanged. Reduction of the *d*-ether with sodium and alcohol gave *products* which possessed negligible light-absorbing properties. However, on addition of one molecule of hydrogen bromide in acetic acid solution, followed by zinc reduction, the *d*-ether was converted into d-*dihydropyrethrolone methyl ether*, the semicarbazone of which gave the corresponding tetrahydro-derivative on hydrogenation. The melting points of the semicarbazones were somewhat indefinite and the optical rotation of the tetrahydro-compound indicated that this was due to partial conversion into the *inactive* modifications during the reaction. This tetrahydro-compound was converted into *i*-tetrahydropyrethrolone methyl ether by treating the semicarbazone with methyl-alcoholic sulphuric acid. Under the same conditions the *i*-pyrethrolone methyl ether gave i-*dihydropyrethrolone methyl ether*, the *semicarbazone* of which was hydrogenated to the corresponding *i*-tetrahydro-derivative. In this case one fraction gave a semicarbazone, m. p. 202—204°, which was shown to be dihydropyrethrone semicarbazone by conversion into dihydrojasmone (tetrahydropyrethrone) on hydrogenation. (The formation of this compound was not observed in the earlier experiments with *d*-pyrethrolone methyl ether, but as it appeared to have no bearing upon the structure of pyrethrolone the experiment with the active ether was not repeated.)



The $\lambda_{max.}$ and ε values for the two dihydro-ethers and the two tetrahydro-derivatives were practically identical and presumably each pair contained similar chromophoric systems. The terminal methyl values for the dihydro-derivatives indicated that the unsaturated group at the end of the chain was present in these compounds. Therefore, it was not possible to use this result to differentiate between the formulæ advanced mainly to bridge the gap between the somewhat conflicting chemical evidence (West, this vol., p. 239) and the requirements of light absorption data (Gillam and West, J., *loc. cit.*). It is, however, clear that (*a*) if (I) is

correct, then reduction to the dihydro-derivative involved addition to the ends of the conjugated system between carbon atoms 4 and 6 with the formation of a double bond between atoms 2 and 3, (*b*) if (II), then addition was made to the ethylenic linkage between carbon atoms 6 and 7, and (*c*) if III, then addition was made to the ends of the conjugated system between carbon atoms 7 and 10. In spite of the great difficulty involved in accepting (III) on the chemical evidence LaForge and Barthel (*loc. cit.*) consider that this formulation, first put forward by Gillam and West (J., 1942, 671), cannot be excluded from consideration. In connection with the various alternative formulæ advanced, the terminal methyl values for samples of the *d*- and the *i*-pyrethrolone methyl ether and their dihydro-derivatives—in spite of the similar absorption data—appear to lend support to the conclusion of LaForge and Barthel (*loc. cit.*) that pyrethrolone may not be a homogeneous substance as previously supposed but a mixture of components differing in the nature of the side chain. This indication that these derivatives of pyrethrolone which show almost identical absorption data can differ in respect to the unsaturation in the side chain appears to be a significant observation and would seem to permit considerable reconciliation of the chemical reactions with the light absorption data. LaForge and Barthel ((*loc. cit.*) found that fractions from pyrethrolone, " pyrethrolone methyl ether," and pyrethrolone acetate had terminal methyl values which indicated heterogeneity, but unfortunately absorption data were not recorded.

The various data are summarised in Table I.

TABLE I.

Absorption Spectra (Alcoholic Solutions) and Terminal Methyl Values for Some Pyrethrolone Derivatives.

	$\lambda_{max.}$, A.	ε.	Terminal methyl value.[1]	M.W. used.
d-Pyrethrolone methyl ether [6]	2275	23,000	0·76	192
d-Dihydropyrethrolone methyl ether [2]	2285	10,900	1·62	194
d-Tetrahydropyrethrolone methyl ether [2]	2305	10,300	—	196
i-Pyrethrolone methyl ether [6]	2270	21,700	0·37	192
i-Dihydropyrethrolone methyl ether [2]	2335	10,800	1·31	194
i-Tetrahydropyrethrolone methyl ether [2]	2305	10,600	—	196
Tetrahydropyrethrolone [3, 2]	2320	12,000	—	182
[4] *d*-Pyrethrolone methyl ether semicarbazone [5]	2320 2665	17,300 19,000	—	249
d-Dihydropyrethrolone methyl ether semicarbazone	2660	19,800	—	251
d-Tetrahydropyrethrolone methyl ether semicarbazone	2650	21,400	—	253
i-Pyrethrolone methyl ether semicarbazone [5]	2320 2655	21,000 19,000	—	249
i-Dihydropyrethrolone methyl ether semicarbazone	2665	20,150	—	251
i-Tetrahydropyrethrolone methyl ether semicarbazone	2660	19,300	—	253
Tetrahydropyrethrolone semicarbazone	2650	22,000	—	239

[1] Expressed as mol. of acetic acid per mol. of the ether. [2] The fact that the light absorption data on these five different compounds are so closely alike points clearly to the presence of the same chromophoric system in the same molecular environment (cf. Gillam and West, J., 1942, 486). Since the dihydro- and the tetrahydro-derivatives are not different, it is clear also that the extra ethylene linkage in the dihydro-derivatives must be isolated from the conjugated system. [3] Gillam and West, J., 1942, 671. [4] The absorption data here are clearly indicative of the presence of the C=C–C≡N chromophore (Evans and Gillam, J., 1943, 565), but this band is less susceptible to the effect of molecular environment than that due to C=C–C=O. [5] West, this vol., p. 239. [6] Data for the samples actually used in preparing the dihydro-ethers (cf. West, this vol., p. 239).

EXPERIMENTAL.

(Analyses are by Drs. Weiler and Strauss, Oxford.)

d-*Tetrahydropyrethrolone Methyl Ether.*—*d*-Pyrethrolone methyl ether (1·1 g.) (West, this vol., p. 241) having b. p. 103°/0·8 mm., $n_D^{20°}$ 1·5034, $[\alpha]_D^{20°}$ + 88° (*c*, 5 in alcohol), OMe 15·85%, dissolved in a mixture of ethyl acetate (45 ml.) and methyl alcohol (45 ml.), was hydrogenated, a platinium oxide catalyst (0·25 g.) being used, absorbing 164 ml. of hydrogen at N.T.P. (Calc. for $C_{13}H_{16}O_2$, 2 double bonds, 256·8 ml.). The filtered solution was concentrated by distillation under reduced pressure, and the residue steam-distilled. The d-*tetrahydropyrethrolone methyl ether* obtained by extraction of the distillate with light petroleum and purified by distillation (0·87 g.) had b. p. 92—93°/1·1 mm., $n_D^{20°}$ 1·4731, $d_{15·5°}^{15·5°}$ 0·966, $[\alpha]_D^{20°}$ + 88° (*c*, 8·37 in alcohol), $\lambda_{max.}$ 2305 A., ε = 10,300 (Found: OMe, 15·1. $C_{13}H_{20}O_2$ requires OMe, 15·8%).

The ether (0·59 g.), dissolved in ethyl alcohol (6 ml.), was mixed with a solution of semicarbazide hydrochloride (0·89 g.) and sodium acetate crystals (1·2 g.) in warm water (1·2 ml.) and kept overnight. Water (50 ml.) was then added, and the mixture refrigerated for 2 hours. The semicarbazone (0·67 g., m. p. 125—130° indef.) crystallised from methyl alcohol (20 ml.) to give 0·15 g., m. p. 137—139°. After one further recrystallisation the d-*tetrahydropyrethrolone methyl ether semicarbazone* had m. p. 141—142°, $[\alpha]_D^{20°}$ −68° (*c*, 0·26 in pyridine), $\lambda_{max.}$ 2650 A., ε = 21,400 (Found: N, 15·3. $C_{13}H_{23}O_2N_3$ requires N, 16·6%).

i-*Tetrahydropyrethrolone Methyl Ether.*—*i*-Pyrethrolone methyl ether (1 g.) (West, J., *loc. cit.*) having b. p. 107—109°/1·5 mm., $n_D^{20°}$ 1·5132, $d_{15·5°}^{15·5°}$ 1·007, $[\alpha]_D^{20°}$ +0·1°, OMe 16·3%, in methyl alcohol (60 ml.), was hydrogenated with a platinum oxide catalyst (0·26 g.), absorbing 215 ml. of hydrogen at N.T.P. (Calc. for $C_{13}H_{16}O_2$ two bonds, 233·5 ml.). The i-*tetrahydropyrethrolone methyl ether* (0·83 g.) (worked up as described for the active ether) had b. p. 95—96°/1·7 mm., $n_D^{20°}$ 1·4732, $d_{15·5°}^{15·5°}$ 0·965, $[\alpha]_D$ ± 0° (*c*, 7·55 in alcohol), $\lambda_{max.}$ 2305 A., ε = 10,600 (Found: OMe, 15·5. $C_{13}H_{20}O_2$ requires OMe, 15·8%).

By the method given for the active compound this ether (0·5 g.) yielded a semicarbazone (0·52 g.), m. p. 115—117°, which was recrystallised from methyl alcohol (15 ml.) to give 0·25 g., m. p. 120—121°. After one further recrystallisation the i-*tetrahydropyrethrolone methyl ether semicarbazone* had m. p. 122—123°, $[\alpha]_D$ ± 0° (*c*, 0·927 in pyridine), $\lambda_{max.}$ 2660 A., ε = 19,300 (Found: N, 15·6. $C_{13}H_{23}O_2N_3$ requires N, 16·6%).

Conversion of the d- *into the* i-*Form.*—The *d*-semicarbazone (1·5 g.), m. p. 140—142°, was refluxed on the water-bath for 2½ hours with a solution of sulphuric acid (0·9 g.) in methyl alcohol (15 ml.); water (15 ml.) was then added, and the bulk of the methyl alcohol removed by distillation under reduced pressure. The residue was saturated with sodium chloride, and the reddish oil extracted with light petroleum. This solution was washed until it was neutral, the solvent removed, and the residue steam-distilled. The oil (0·7 g.) extracted from the distillate with light petroleum had b. p. 90°/1·2 mm., $n_D^{20°}$ 1·4747, $d_{15·5°}^{15·5°}$ 0·968, $[\alpha]_D \pm 0°$ (*c*, 2 in alcohol), of which the semicarbazone, after recrystallisation from methyl alcohol, had m. p. 122—124°, $[\alpha]_D \pm 0°$ (*c*, 1 in pyridine); the m. p. was not depressed by admixture with the semicarbazone, m. p. 122—123°, prepared from *i*-tetrahydropyrethrolone methyl ether.

d-*Dihydropyrethrolone Methyl Ether.*—*d*-Pyrethrolone methyl ether (7·3 g.), b. p. 115—117°/1·8 mm., $n_D^{20°}$ 1·5136, $d_{15·5°}^{15·5°}$ 1·004, $[\alpha]_D^{20°}$ + 87·2°, OMe 15·7%, terminal methyl value 0·76 (expressed as mol. of acetic acid per mol. of ether), $\lambda_{max.}$ 2275 A., $\varepsilon = 23{,}000$, was dissolved in glacial acetic acid (36·5 ml.), and the solution cooled in ice. Hydrogen bromide (previously washed by passing through acetic acid and then over calcium chloride) was passed slowly through until the weight had increased by 3·3 g. (1 mol. of hydrogen bromide ≡ 3·1 g.). The apparatus was disconnected and kept at laboratory temperature overnight with calcium chloride tubes fixed at the exit points. Acetic acid (36 ml.) was added, followed by zinc dust (20 g.) in approximately 3 g. portions during 2 hours, to the mechanically stirred solution heated under reflux on the water-bath. Cold water (500 ml.) was added to the cooled solution, which was then saturated with sodium chloride, and the oil extracted with ether. The ethereal solution was washed with cold N/10-sodium carbonate until neutral (sodium chloride being added at each washing) and finally with water, and the solvent removed by distillation to leave an orange-coloured oil, which was steam-distilled. The practically colourless oil (5·0 g.) extracted from the distillate with light petroleum was carefully fractionated in a 10 ml. flask with a vacuum-sealed fractionating column (Shrader and Ritzer, *Ind. and Eng. Chem. Anal.*, 1939, **11**, 54).

Fraction.	B. p./0·7 mm.	$n_D^{20°}$.	Wt. (g.).	$\lambda_{max.}$, A.	$\varepsilon_{max.}$	Mol. wt. taken.
1	<72°	1·4965	0·28	—	—	—
2	79—81	1·4965	2·55	2290	11,500	194
3	82—85	1·4983	0·58	—	—	—
4	86—95	1·5028	1·08	—	—	—
Residue	—	—	0·45	—	—	—

Fraction 2 (2·45 g.), dissolved in alcohol (25 ml.), was added to a solution of semicarbazide hydrochloride (3·67 g.) and crystalline sodium acetate (4·5 g.) in water (5 ml.). After refrigeration overnight the first crop of crystals (2·6 g.) had m. p. 156—170° (sintering at 145°) and a second crop (0·3 g.), obtained by adding water (25 ml.) and refrigeration, had m. p. 152—165° (sintering at 143°). Fraction 1 (0·17 g.) under similar conditions yielded a semicarbazone (0·15 g.), m. p. 156—170° (sintering at 145°). These semicarbazones were bulked (3·0 g.) and recrystallised from benzene (65 ml.) to give a first crop (2·2 g.), m. p. 161—167°. Recrystallised from benzene (50 ml.), the product (1·7 g.) had m. p. 163—168°. This was recrystallised from methyl alcohol (50 ml.) to give d-*dihydropyrethrolone semicarbazone* (1·2 g.) as powdery white crystals, m. p. 175° (sintering at 169°), $[\alpha]_D^{20°}$ −51·8° (*c*, 1·1 in pyridine), $\lambda_{max.}$ 2660 A., $\varepsilon_{max.}$ 19,800 (Found: N, 16·0. $C_{13}H_{21}O_2N_3$ requires N, 16·7%). (The m. p.'s were indefinite and there is little doubt that partial conversion of the *d*-pyrethrolone methyl ether into the inactive ether was brought about by the acid treatment so that the *d*-dihydro-derivative and its semicarbazone were not optically pure.) This semicarbazone (0·47 g.) in ether (20 ml.) was shaken during 8 days in a mechanical shaker with a solution of potassium hydrogen sulphate (7 g.) in water (20 ml.) in an atmosphere of carbon dioxide. The ethereal solution was separated and washed successively with brine and water, the solvent removed, and the oil distilled to give regenerated d-*dihydropyrethrolone methyl ether* (0·28 g.), b. p. 95—96°/2 mm., $n_D^{20°}$ 1·4947, $d_{15·5°}^{15·5°}$ 0·980, $[\alpha]_D^{20°}$ + 70·8° (*c*, 6·75 in alcohol), $\lambda_{max.}$ 2285 A., $\varepsilon_{max.}$ 10,900 (Found: OMe, 15·2. $C_{12}H_{18}O_2$ requires OMe, 16·0%). The terminal methyl value is 1·62, expressed as mol. of acetic acid per mol. of ether (LaForge and Barthel, *loc. cit.*). This product gave a semicarbazone which after recrystallisation from methyl alcohol had $[\alpha]_D$ − 60° (*c*, 0·27 in pyridine), m. p. 176° (sintering at 171°), not depressed by admixture with the semicarbazone before regeneration treatment. Dihydropyrethrolone methyl ether semicarbazone (0·5 g.) in methyl alcohol (120 ml.) was hydrogenated with a previously reduced platinum oxide catalyst (≡ 0·1 g. of PtO_2), absorbing 51·9 ml. of hydrogen at N.T.P. in 3 minutes with no further absorption after 15 minutes ($C_{13}H_{21}O_2N_3$, one double bond, requires 44·6 ml. at N.T.P.). The filtered solution was concentrated by distillation under reduced pressure to 5 ml. and refrigerated to give white crystals (0·38 g.), m. p. 116° (sintering at 104°). Recrystallised twice from benzene, the product (0·22 g.) had m. p. 119° (sintering at 108°); recrystallisation from ether (4 ml.) then gave 0·17 g., m. p. 121° (sintering at 110°), $[\alpha]_D^{20°}$ − 39° (*c*, 1·1 in pyridine). This was shown to be optically impure *d*-tetrahydropyrethrolone methyl ether semicarbazone by conversion into the *i*-semicarbazone. This *d*-semicarbazone with some second crop (0·4 g.) in methyl alcohol (5 ml.) containing sulphuric acid (0·25 g.) was heated on the water-bath during 2 hours. Water was added, the mixture saturated with sodium chloride, and the oil extracted with light petroleum. The oil recovered (0·13 g.), $n_D^{20°}$ 1·4731, gave by the usual method a semicarbazone (0·16 g.), m. p. 115—119°, which was raised by one recrystallisation from methyl alcohol to 121—122°, not depressed by admixture with the semicarbazone, m. p. 122—123°, of *i*-tetrahydro-pyrethrolone methyl ether.

Fractions 3 and 4 were converted into semicarbazones and worked up, but it was not possible to separate completely the mixture of *d*- and *i*-ethers and their dihydro-derivatives which appeared to comprise these fractions. No evidence was obtained in any experiments for the presence of an isomeric dihydro-ether, *i.e.*, one in which the double bond nearest the ring was intact.

i-*Dihydropyrethrolone Methyl Ether.*—*i*-Pyrethrolone methyl ether (10 g.), b. p. 108—110°/1·8 mm., $n_D^{20°}$ 1·5106, $[\alpha]_D^{20°}$ +0·3°, OMe 15·7%, terminal methyl value 0·37 (expressed as mol. of acetic acid per mol. of ether), $\lambda_{max.}$, 2270 A., ε = 21,700, in acetic acid (50 ml.) was treated with hydrogen bromide (4·2 g.) (1 mol. HBr ≡ 4·22 g.) and worked up as described for *d*-dihydropyrethrolone methyl ether, but 25 g. of zinc dust were used. The steam-volatile oil (6·35 g.) was fractionated in a 20 ml. fractionating flask:

Fraction.	B. p./0·7 mm.	$n_D^{20°}$.	Wt. (g.).
1	<72°	1·4895	0·1
2	79—81	1·4960	0·65
3	81—82	1·4975	0·61
4	82—86	1·4980	1·44
5	86—90	1·5007	0·47
6	90—98	1·5068	1·49
Residue	—	—	1·0

Fraction 1 yielded a semicarbazone, m. p. 155° (indef., sintering at 140°), which was not further examined.

Fraction 2 (0·58 g.) in alcohol (6 ml.) was added to a solution of semicarbazide hydrochloride (0·87 g.) and sodium acetate crystals (1·18 g.) in water (1·2 ml.), and the mixture refrigerated overnight. The white crystalline solid which separated (0·56 g.) had m. p. 174° (indef., sintering at 145°) and when recrystallised from methyl alcohol (35 ml.) the product (0·35 g.) had m. p. 185° (sintering at 171°). After two further recrystallisations from methyl alcohol the crystals (0·12 g.) had m. p. 202—204° (decomp.). This semicarbazone (50 mg.), dissolved in methyl alcohol (20 ml.), was hydrogenated with a reduced platinum catalyst (≡ 30 mg. of PtO_2), absorbing 5·2 ml. of hydrogen at N.T.P. in 3 minutes with no further absorption after 20 minutes (Calc. for $C_{12}H_{19}ON_3$, one double bond, 5·1 ml.). The filtered solution was concentrated under reduced pressure to 5 ml., water (5 ml.) added, and the mixture refrigerated overnight. The white crystals which separated (40 mg.) had m. p. 173° (sintering at 169°), raised by one recrystallisation from benzene to 174—175°, not depressed by admixture with authentic dihydrojasmone semicarbazone, m. p. 175—176° [prepared from tetrahydropyrethrolone *via* the corresponding chloro-compound as described by LaForge and Haller (*J. Amer. Chem. Soc.*, 1936, **58**, 1777)].

Fractions 3 and 4 were bulked (1·95 g.) and, when treated as above (addition of water and refrigeration), yielded a semicarbazone (2·2 g.), m. p. 168° (indef., sintering at 159°), which was recrystallised from methyl alcohol (40 ml.) to give white crystals (1·4 g.), m. p. 170° (sintering at 166°). After three further recrystallisations the *semicarbazone* of *i*-dihydropyrethrolone methyl ether (0·95 g.) had m. p. 185° (sintering at 181°), $[\alpha]_D \pm 0°$ (*c*, 1·0 in pyridine), $\lambda_{max.}$ 2665 A., $\varepsilon = 20{,}150$ (Found: N, 16·8. $C_{13}H_{21}O_2N_3$ requires N, 16·7%). This semicarbazone (0·35 g.), dissolved in methyl alcohol (50 ml.), was hydrogenated in the presence of a platinum oxide catalyst (0·2 g.), previously reduced, absorbing 30·3 ml. of hydrogen at N.T.P. after 5 minutes, with no further absorption after 20 minutes ($C_{13}H_{21}O_2N_3$, one double bond, requires 31·2 ml. at N.T.P.). The filtered solution was concentrated under reduced pressure to 7 ml., water (10 ml.) added, and the mixture refrigerated. The crystalline product obtained (0·32 g.) had m. p. 118—120° (sintering at 116°), raised by one recrystallisation to 121—122°, not depressed by admixture with the semicarbazone of *i*-tetrahydropyrethrolone methyl ether. An ethereal solution of the semicarbazone of *i*-dihydropyrethrolone methyl ether (0·5 g.) was shaken with a concentrated aqueous solution of potassium hydrogen sulphate for 10 days in an atmosphere of carbon dioxide and worked up as described for the *d*-compound. The regenerated *i-dihydropyrethrolone methyl ether* (0·18 g.) had b. p. 78—80°/1·8 mm., $n_D^{20°}$ 1·4976, $d_{15·5°}^{15·5°}$ 0·985, $[\alpha]_D \pm 0°$ (*c*, 4·0 in pyridine), $\lambda_{max.}$ 2335 A., $\varepsilon = 10{,}800$ (Found: OMe, 15·4. $C_{12}H_{18}O_2$ requires OMe, 16·0%). The terminal methyl value is 1·31, expressed as mol. of acetic acid per mol. of ether. The semicarbazone derived from this product, after one recrystallisation from methyl alcohol, had m. p. 185° (sintering at 183°), $[\alpha]_D \pm 0°$. The m. p. was not depressed by admixture with the parent semicarbazone, showing that no change had taken place during regeneration.

Fraction 5 (0·4 g.) gave a semicarbazone (0·42 g.), m. p. 178° (sintering at 166°). After four recrystallisations from methyl alcohol the product (0·14 g.) had m. p. 196—197°, not depressed by admixture with authentic *i*-pyrethrolone methyl ether semicarbazone, m. p. 197—198°.

Fraction 6 (1·4 g.), treated with semicarbazide in the usual manner, yielded a semicarbazone (1·4 g.), m.p. 167° (indef., sintering at 145°). After three recrystallisations from methyl alcohol the product (0·6 g.) had m. p. 195—196°, not depressed by admixture with authentic *i*-pyrethrolone methyl ether semicarbazone, m. p. 197—198°.

Reduction of d-*Pyrethrolone Methyl Ether with Sodium and Alcohol.*—*d*-Pyrethrolone methyl ether (8·5 g.), b. p. 122—124°/4·5 mm., $n_D^{20°}$ 1·5113, $[\alpha]_D + 83·9°$, $\lambda_{max.}$ 2260 A., $\varepsilon = 23{,}400$, was dissolved in alcohol (90 ml.), and sodium (11 g.) added under reflux during 25 minutes. Then alcohol (30 ml.) was added, and the flask heated on the water-bath until all the sodium had dissolved. Water (20 ml.) was added, and the alcohol removed by steam-distillation, followed by steam-distillation of the oil. This oil was extracted from the distillate with light petroleum, and the oil recovered therefrom (5·8 g.) treated with semicarbazide in the usual manner, but no semicarbazone was obtained. The oil, which was recovered quantitatively (5·76 g.), was distilled to give two fractions: (i) 4·2 g., b. p. 95—102°/5·5 mm., $n_D^{20°}$ 1·4715, $d_{15·5°}^{15·5°}$ 0·9232, $[\alpha]_D + 1°$ (Found: C, 74·2; H, 11·4; OMe, 6·25%), $\lambda_{max.}$ 2380 A., $E_{1\,cm.}^{1\%}$ 21·3, showing that no conjugated system was now present in the molecule but that absorption was due to a trace of conjugated material only. Under conditions similar to those employed for the preparation of *d*-pyrethrolone methyl ether with methyl sulphate (West, this vol., p. 239) this product gave a methylation product, b. p. 75—78°/2·5 mm., $n_D^{20°}$ 1·4610, $\lambda_{max.}$ 2380 A., $E_{1\,cm.}^{1\%} = 11·3$ (Found: OMe, 10·85%), and an acetylation product, b. p. 75—78°/2 mm., $n_D^{20°}$ 1·4564, $\lambda_{max.}$ 2360 A., $E_{1\,cm.}^{1\%} = 11·1$ (Found: C, 75·7; H, 10·8%). Fraction (ii) (0·5 g.) had b.p. 102—120°/5·5 mm., $n_D^{20°}$ 1·4700, $[\alpha]_D + 2°$ (*c*, 2 in alcohol), $\lambda_{max.}$ 2380 A., $E_{1\,cm.}^{1\%} = 19·7$ (Found: C, 72·1; H, 11·3; OMe, 13·0%).

Treatment of d- *and* i-*Ethers with Aluminium Amalgam.*—*d*-Pyrethrolone methyl ether (2 g.), b. p. 115—117°/1·8 mm., $[\alpha]_D^{20°} + 87·2$, OMe 15·7%, in ethereal solution (120 ml.) was poured on amalgamated aluminium (6 g.) prepared as described by LaForge and Haller (*J. Org. Chem.*, 1938, **2**, 552). By proceeding essentially as described by these authors, the following fractions were obtained:

Fraction.	B. p./0·8 mm.	$n_D^{20°}$.	Wt. (g.).	M. p. of semicarbazone (after recrystallisation from methyl alcohol).
1	80—85°	1·5071	0·15	176—180°
2	85—86	1·5105	0·23	182—183
3	87—92	1·5172	0·27	182—183
4	92—94	1·5210	0·49	182—184
Residue	—	—	0·4	—

The m. p.'s of the semicarbazones were not depressed on admixture with the semicarbazone, m. p. 183—184°, prepared from the original *d*-pyrethrolone methyl ether.

i-Pyrethrolone methyl ether (5 g.), b. p. 108—110°/1·8 mm., $[\alpha]_D + 0·3°$, OMe 15·7%, in ether (300 ml.), treated with amalgamated aluminium (15 g.), gave two fractions: (*a*) 2 g., b. p. 84—86°/0·9 mm., $n_D^{20°}$ 1·5090, (*b*) 2·4 g., b. p. 86—89°/0·9 mm., $n_D^{20°}$ 1·5110. Fraction (*a*) gave a semicarbazone, m. p. 196—198° after recrystallisation from methyl alcohol, and fraction (*b*) a semicarbazone, m. p. 197—198°, of which the m. p.'s were not depressed on admixture with the semicarbazone, m. p. 197—198°, prepared from the original *i*-pyrethrolone methyl ether.

Determinations of absorption spectra were made in ethyl alcohol solutions on a Hilger E_3 quartz spectrograph in conjunction with a Spekker photometer.

I am greatly indebted to Dr. A. E. Gillam, F.R.I.C., for his kindness in making available the absorption data and to the Directors of Messrs. Stafford Allen and Sons, Ltd., for facilities.

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176. *Studies on Hydrogen Cyanide. Part XIV. Formamidodichloride.*

By L. E. Hinkel and T. I. Watkins (with K. M. Jones).

Formamidodichloride is produced during the action of hydrogen chloride on hydrogen cyanide in which the final product is the crystalline dichloromethyleneformamidine hydrochloride (sesquichloride). An explanation is now offered for the mode of formation of the latter compound. The presence of formamidodichloride was established through its condensation with nitrobenzaldehydes, whereby nitrobenzylidenebisformamides were ultimately obtained, and the identity of these compounds was confirmed by synthesis from formamide.

It is only after hydrogen chloride has been passed for a long time into a solution of hydrogen cyanide in ether that any change becomes apparent by the deposition of the solid sesquichloride of hydrogen cyanide (Hinkel and Dunn, J., 1930, 1836; Hinkel, Ayling, and Beynon, J., 1936, 185). No explanation has hitherto been offered for the formation of the sesquichloride, but it is probably the result of several reactions in which the union of hydrogen cyanide with hydrogen chloride to form formimidochloride (I) may be the primary stage.

In order to account for the formation of the hydrochlorides of the formimido-ethers and the phenolic aldimines by the action of hydrogen chloride on hydrogen cyanide in the presence of alcohols and phenols, respectively, Pinner and Klein (*Ber.*, 1878, **11**, 1475) and Gattermann (*ibid.*, 1898, **31**, 1149) presumed the primary action to be the formation of formimidochloride. This compound has, however, not been isolated, and it would seem that, if it does exist in solution it readily decomposes into its components with increase in dilution, since dilute solutions of hydrogen cyanide and hydrogen chloride in equimolecular proportion can be kept for a long time without undergoing any apparent change. When resorcinol is added to such dilute ethereal solutions, a small amount only of the insoluble aldimine hydrochloride is deposited, indicating that very considerable decomposition of formimidochloride must have occurred, since with increase in concentration of one or both of the reactants the yield of aldimine hydrochloride is also much increased (see Tables I and II). With increase in the concentration of the two reactants, hydrogen cyanide and chloride, not only is there an apparent increase in formimidochloride but further changes also occur, since some crystalline " sesquichloride," which is insoluble in ether, begins to be deposited. The greater the concentration, the greater the yield of the sesquichloride.

Since the formation of the sesquichloride requires two molecules of hydrogen cyanide for three molecules of hydrogen chloride, the supernatant liquid becomes relatively richer in hydrogen cyanide; nevertheless, there is always free hydrogen chloride in solution and the formation of the sesquichloride is never complete. Furthermore, complete formation of the sesquichloride does not occur when the original proportion of hydrogen cyanide to hydrogen chloride is 2 : 3 or even more.

The changes occurring with increase in the concentration of formimidochloride cannot be primarily a simple union of two molecules of the latter to give chloromethyleneformamidine (II) as below, since this compound does not further combine with hydrogen chloride (cf. Hinkel and Dunn, *loc. cit.*).

$$\text{(I.)}\quad 2NH{:}CHCl = NH{:}CH{\cdot}N{:}CHCl\ \text{(II.)} + HCl$$

The existence of two chlorine atoms on the terminal carbon atom of the sesquichloride therefore suggests formamidodichloride, dichloromethylamine (III), to have been formed at one period. The existence of that compound would readily account for the formation of the sesquichloride through the union of two of its molecules :

$$\text{(III.)}\quad 2NH_2{\cdot}CHCl_2 = NH_2{\cdot}CHCl{\cdot}NH{\cdot}CHCl_2 + HCl$$

Several examples of the existence of amidodichlorides and their derivatives exist among aromatic compounds (Wallach, *Annalen*, 1877, **184**, 4; Pinner and Klein, *Ber.*, 1879, **12**, 97). These amidodichlorides in general are unstable substances whlch are transformed into imidochlorides by loss of hydrogen chloride. On the other hand, several substituted imidochlorides are known which unite directly with halogen halides, yielding crystalline dihalogen amides (Stephen and Bleloch, J., 1931, 888; Lander and Law, J., 1904, **85**, 1695; Franzen and Henglein, *J. pr. Chem.*, 1915, **91**, 245). A crystalline acetamidodichloride has also been prepared by the action of hydrogen chloride on acetonitrile (unpublished work).

The presence of formamidodichloride was made evident through its condensation product with the nitrobenzaldehydes, since it has been shown (Reich and Richben, *Monatsh.*, 1904, **25**, 933) that amides react with aldehydes, giving rise to three classes of derivative (IV, V, VI) according to the conditions employed.

$R{\cdot}CH{:}N{\cdot}COR'$ (IV.)	$R{\cdot}CH(OH){\cdot}NH{\cdot}COR'$ (V.)	$R{\cdot}CH(NH{\cdot}COR')_2$ (VI.)
$NO_2{\cdot}C_6H_4{\cdot}CH(NH{\cdot}CHCl_2)_2$ (VII.)	$NO_2{\cdot}C_6H_4{\cdot}CH(NH{\cdot}CHO)_2$ (VIII.)	$NO_2{\cdot}C_6H_4{\cdot}CH{:}N{\cdot}CHO$ (IX.)

The condensation products of formamidodichloride could not be isolated in the pure state owing to their instability, but they appear to be of the type (VI) and to possess the structure (VII), since on carefully regulated hydrolysis they yielded the corresponding *nitrobenzylidenebisformamides* (VIII). The identity of these bisformamides was confirmed by their synthesis from the corresponding nitrobenzaldehydes and formamide (cf. Ytterah and Pandy, *Proc. Indian Acad. Sci.*, 1942, **15**, *A*, 256).

No condensation occurs between the nitrobenzaldehydes and formamide in benzene, dioxan, or alcoholic solution, but does so readily when formamide is replaced by its hydrochloride. Under these conditions the bisformamides of *m*- and *p*-nitrobenzaldehydes have been obtained, m. p. 178° and 192°, respectively. Ytterah and Pandy (*loc. cit.*) give the m. p. of the *m*-derivative as 168° but it is doubtful whether they obtained the pure compound, since *m*-nitrobenzaldehyde, when heated with formamide under the conditions described by them, yields a monoformamide (IX), m. p. 158°.

The bisformamido-compounds are very readily hydrolysed by dilute acids even in the cold. The *p*-derivative presents an unusual feature, for, whenever obtained from formamidodichloride, the specimen, even after several recrystallisations, melts at 192° to a clear colourless liquid. On being kept for many weeks, the compound gradually changes into a *dimer*, the m. p. slowly falling and being finally replaced by a decomposition point about 160° with the formation of a deep red product. When synthesised from formamide hydrochloride, a crude specimen could be obtained, m. p. 192°, but this product more often than not would yield the dimer after one crystallisation.

Experimental.

Effect of Dilution on Aldimine Formation.—A solution of dry hydrogen chloride in dry ether was prepared (24 g. per 100 c.c.), and by its means four mixtures were prepared containing unimolecular quantities of hydrogen chloride, hydrogen cyanide, and resorcinol in various quantities of dry ether. The mixtures were kept at 0° for several hours, and then allowed gradually (18 hours) to reach 10°. After the supernatant liquids had been poured off, the semi-solid deposits were washed with ether by decantation and dissolved in water. The aqueous solutions of the aldimine hydrochlorides were then hydrolysed by gentle boiling for 10 minutes, cooled, and extracted with ether. After the extracts had been dried and the ether removed, the residues of resorcylaldehyde were weighed.

Table I.

In each expt., 0·1 g.-mol. each of HCl (15 c.c. of solution), HCN (4 c.c.), and resorcinol (11 g.) was used. The calculated yield is 13·8 g.

Added ether, c.c.	74	54	34	4
Total vol., c.c.	100	80	60	30
Yield of aldehyde, g.	0·7	1·6	3·9	7·2

Effect of Excess of Hydrogen Cyanide on Aldimine Formation.—By means of an ethereal solution of hydrogen chloride containing 21 g. in 100 c.c., two solutions were prepared containing unimolecular quantities of hydrogen chloride and resorcinol with four molecular quantities of hydrogen cyanide at two different dilutions in ether, and for comparison a similar set was made employing unimolecular quantities of each reactant at corresponding dilutions. The conditions of the experiment and the method of analysis were as previously described.

Table II.

In each expt., 0·1 g.-mol. each of HCl (17 c.c. of solution) and resorcinol (11 g.) was used. The calculated yield is 13·8 g.

HCN, c.c. (equiv. to 0·1 g.-mol.)	16	16	4	4
Added ether, c.c.	0	10	12	22
Total vol., c.c.	40	50	40	50
Yield of aldehyde, g.	9·4	8·7	6·6	4·7

Condensation of Formamidodichloride with m-*Nitrobenzaldehyde.*—To a solution of *m*-nitrobenzaldehyde (15 g.; 1 mol.) in dry ether (35 c.c.) hydrogen cyanide (8·1 c.c.; 2 mols.) was added. The ice-cooled solution was saturated with hydrogen chloride, and the mixture left overnight, a thick viscous liquid separating. The supernatant ether was decanted, the semi-solid residue washed with ether, triturated with a little crushed ice and water, and the solid thus formed, filtered off and washed with alcohol and then with benzene. The product was dried in air and crystallised from hot alcohol; m. p. 178°, unchanged by admixture with a synthesised specimen of m-*nitrobenzylidenebisformamide* (Found: C, 48·5; H, 3·9; N, 18·85. $C_9H_9O_4N_3$ requires C, 48·4; H, 4·0; N, 18·8%) (see below).

m-*Nitrobenzylidenebisformamide.*—A solution of *m*-nitrobenzaldehyde (5 g.; 1 mol.) and formamide (10 g.; 6 mols.) in ether (20 c.c.) was saturated with hydrogen chloride at 0°. The resulting thick liquid was left overnight, and then gently warmed on the water-bath to decompose the excess of formamide. The solid deposit of ammonium chloride so formed was removed, and the filtrate evaporated to semi-dryness on the water-bath, during which much hydrogen chloride was evolved. The solid was triturated with a few c.c. of ice-water and washed with alcohol, followed by ether. The crude product melted at 166—175° and was crystallised from hot alcohol, yielding colourless prisms, m. p. 178° (Found: C, 48·2; H, 4·0; N, 18·5%).

Condensation of Formamidodichloride with p-*Nitrobenzaldehyde.*—Since *p*-nitrobenzaldehyde is only sparingly soluble in ether, the condensation was carried out in dioxan. Into an ice-cooled solution of *p*-nitrobenzaldehyde (7·5 g.; 1 mol.) and hydrogen cyanide (4 c.c.; 2 mols.) in dioxan (21 g.), hydrogen chloride was passed until the gain in weight was 11 g. (6 mols.), and the mixture left overnight. On addition of an excess of ether to the clear yellow liquid, a viscous liquid was precipitated. The supernatant liquid was decanted, and the viscous product redissolved in the minimum of dioxan and reprecipitated by ether. The semi-solid product was treated as in the previous experiment and crystallised from hot alcohol, *p*-nitrobenzylidenebisformamide being obtained as colourless crystals, m. p. 192° unchanged by admixture with an authentic specimen. After several weeks, the m. p. of the compound gradually fell to *ca.* 170°. The change was accelerated by repeated crystallisation from methyl alcohol–dioxan, transparent crystals being obtained which decomposed without melting at 160° with evolution of gas, forming a red solid of high m.p. [*M*, by Rast's camphor method, 462. $(C_9H_9O_4N_3)_2$ requires *M*, 458].

p-*Nitrobenzylidenebisformamide.*—Synthesised as for the *m*-compound except that the ether was replaced by 10 c.c. of dioxan, this compound melted at 192°, but unlike that prepared from formamidodichloride it was sensitive to change on crystallisation and often after one crystallisation was converted into the foregoing *dimer*.

University College, Swansea. [*Received, September 22nd*, 1944.]

177. *The Kinetics of the Sulphonation of Some Aromatic Compounds by Sulphur Trioxide.*

By (Miss) E. Dresel and C. N. Hinshelwood.

The kinetic investigation of the sulphonation of aromatic compounds by sulphur trioxide in solutions of nitrobenzene (Vicary and Hinshelwood, J., 1939, 1372; Wadsworth and Hinshelwood, this vol., p. 469) has been extended to the reactions of benzene, bromobenzene, *m*-dichlorobenzene, α-nitronaphthalene, and *p*-nitroanisole. All reactions are found to be of the second order with respect to sulphur trioxide, and to exhibit the characteristic retardation by the product. The first order with respect to the aromatic reactant, which had been anticipated, has now been confirmed experimentally. Except with *p*-nitroanisole, the effects of substituents on the rate of sulphonation have been accounted for by changes in activation energy, and a correlation is found between such changes and the electronic effects of substituents as measured by dipole moments.

In the study of aromatic substitution reactions we are confronted with two main problems which, it appears, could best be solved by a kinetic investigation of such processes. The first is the specific mechanism of substitution in aromatic compounds, and about this little information is available. The second problem is concerned with physical interpretation of the postulates of the electronic theory of organic reactions with regard to the effects of substituents on the rate of further substitution (Robinson, *J. Soc. Dyers Col.*, Jubilee Issue, 1934, 65; Ingold, J., 1927, 2918; *Chem. Rev.*, 1934, **15**, 225). Some light has been thrown on the latter aspect by work in the field of dipole moments (Sutton, *Proc. Roy. Soc.*, 1931, **133**, *A*, 668; Ri and Eyring, *J. Chem. Physics*, 1940, **8**, 433). Furthermore, with various reactions of substituted aliphatic compounds, Hinshelwood, Laidler, and Timm (J., 1938, 848) have shown a correlation between changes in activation energy and the effects of substituents as postulated by the electronic theory of organic reactions.

For aromatic substitution reactions, kinetic data are difficult to obtain, since the usual experimental conditions are unsuitable for quantitative work and the reactions are generally complex (cf. Benford and Ingold, J., 1938, 929).

Some interesting results, however, emerged from the work begun by Vicary and Hinshelwood (*loc. cit.*) and continued by Wadsworth and Hinshelwood (*loc. cit.*) and by H. Paneth (unpublished). In the course of this series of investigations the kinetics of the sulphonation by sulphur trioxide were studied first with nitrobenzene and then with *p*-nitrotoluene and chlorobenzene in a medium of nitrobenzene. All three reactions showed similar characteristic features, *viz.*, the second order with respect to sulphur trioxide and a marked retardation by the sulphonic acid produced. The second order suggested a mechanism of substitution involving either one molecule of S_2O_6, which must be supposed to exist in equilibrium, in small amounts, with the monomeric form, or the simultaneous action of two single SO_3 molecules. With regard to the effects of substituents, the evaluation of the parameters of the Arrhenius equation showed that the changes in the rate of sulphonation were due to differences in activation energy rather than to a change in the probability of reaction, the value of the *P* factor being similar in the three cases. It is, however, desirable to obtain kinetic data for the reactions of other aromatic derivatives before drawing any far-reaching conclusions. The reaction of the unsubstituted compound, benzene itself, is of great interest. The halogenobenzenes which, owing to their *op*-directing power coupled with a decrease in nuclear reactivity, have sometimes been said to behave abnormally, also merit special attention.

In the present work we have, therefore, carried out kinetic studies under similar conditions with benzene, bromobenzene, and *m*-dichlorobenzene. [Some preliminary work had already been done on the benzene reaction by H. Paneth (unpublished), indicating a second order with respect to SO_3 and a rough value of 5500 cals. for the activation energy.] After a preliminary investigation of various other simple aromatic derivatives, α-nitronaphthalene and *p*-nitroanosole were selected as the only suitable compounds for this type of work. The experimental difficulties, which had always been appreciable, were accentuated by the high speeds of most reactions studied in the present work, but in view of the inherent interest attached to kinetic data for substitution reactions of a series of benzene derivatives, the application of the original method of investigation to these fast reactions appeared justified in spite of the inevitably large experimental errors. Nitrobenzene was retained as the medium so that it would be possible to compare the kinetics of all reactions under similar solvent conditions. No correction for the sulphonation of the solvent was required, since all rates measured here were 10^2 to 10^4 times as fast as that of nitrobenzene.

Experimental.

(a) *Reagents and Apparatus.*—Nitrobenzene, bromobenzene, *m*-dichlorobenzene, benzene, α-nitronaphthalene, and *p*-nitroanisole were all redistilled or recrystallised to constant b. p. or m. p. A fresh solution of sulphur trioxide in nitrobenzene was prepared for each run from 65% fuming sulphuric acid, by carrying sulphur trioxide fumes from the surface of the oleum into the nitrobenzene by means of a current of air. Work at 25° and 40° was done in electrically heated and stirred water-baths. At the low temperature, about 3°, a semi-solid slush of freezing benzene in a Dewar vessel was used as the thermostat. End-point measurements were carried out, as before, at 121° in an oil-bath heated by boiling perchloroethylene.

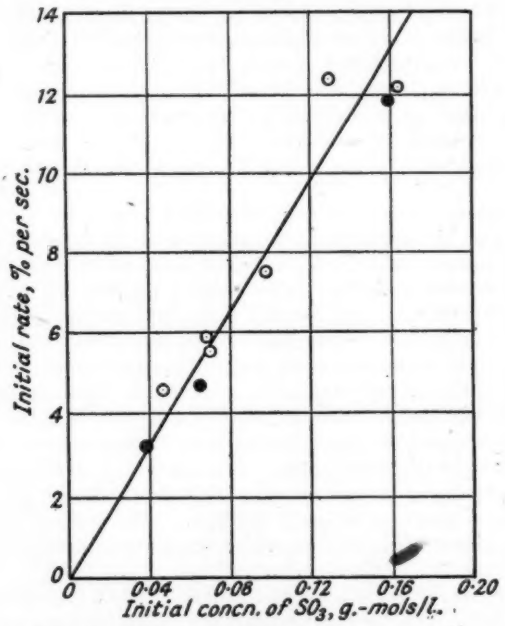
(b) *Observation of the Course of Reaction.*—The method used for following the progress of the reaction with time did not differ in principle from that previously described. All reaction rates measured in the course of the present investigation were faster than those found for *p*-nitrotoluene, and with benzene, faster even than the chlorobenzene reaction. A form of inverted Y-tube was used as the reaction vessel, 2-c.c. portions of the aromatic and the sulphur trioxide

solution being pipetted into the respective limbs. 5-C.c. portions were used for the faster reactions, especially for benzene, in order to increase the accuracy with which titres could be determined at the very low sulphur trioxide concentrations which had to be used. When the reagents contained in the Y-tube had attained the required temperature in the thermostat, the reaction was started by tilting and shaking the tube. After a suitable reaction time, which was recorded by means of an accurate stop-watch, the reaction was arrested suddenly by pouring the contents of the tube into about ten times the volume of electrically stirred water which contained excess alkali. The titration of the resulting emulsion was carried out with N/50-sodium hydroxide and hydrochloric acid, the end-point being approached from both sides and the solution shaken vigorously after each addition of acid or alkali. Bromothymol-blue was used as indicator.

The acidity at the beginning of reaction was obtained by titrating the contents of a tube containing 2 c.c. of the sulphur trioxide solution only, the same procedure being adopted for filling, preheating, and emptying the tube as was used for the rate measurements. Reaction end-points were determined by heating equal volumes of pure nitrobenzene and sulphur trioxide solution at 121° for 24 hours.

Results.—(a) *Order with respect to sulphur trioxide.* The extent of reaction was expressed as a percentage of the total change and plotted against the reaction time. The reaction curves all become almost parallel to the time axis after about 50% change, as was found by previous workers. From the slopes of the tangents drawn to the reaction-time curves at the origin, the initial rates of change were deduced. For a given concentration of the aromatic reagent initial rates (in % per sec.) were plotted against the sulphur trioxide concentrations. The straight lines passing through the origin (see Fig. 1) pointed to the second-order nature of the reaction with respect to sulphur trioxide. From the slopes of these lines, the measured velocity constants, k', were calculated at each temperature (Table I).

FIG. 1.



⊙ *Runs with initial concentration of α-nitronaphthalene* = 0·25 *g.-mol./l.*
● " " " " " " " = 0·10 " (*Plotted rates* = 2·5 × *measured rates.*)

TABLE I.

Velocity constants at different temperatures.

Compound.	Temp.	Concn. of aromatic compd. (g.-mol./l.).	Mean k' (l./g.-mol. sec.).
Benzene	3·1°	0·05	0·86
	40·1	0·05	2·44
Bromobenzene	3·1	0·25	0·97 × 10^{-1}
	40·1	0·25	5·26 × 10^{-1}
m-Dichlorobenzene	1·9	0·50	0·275 × 10^{-2}
	40·1	0·50	2·18 × 10^{-2}
α-Nitronaphthalene	3·3	0·25	1·47 × 10^{-1}
	25·1	0·25	3·25 × 10^{-1}
	40·1	0·25	8·17 × 10^{-1}
p-Nitroanisole	2·0	0·10	2·41 × 10^{-1}
	40·1	0·10	6·29 × 10^{-1}

(b) *Order with respect to aromatic reagent.* With bromobenzene, α-nitronaphthalene, and *p*-nitroanisole, experiments were made at two different concentrations of the aromatic reagent. The reaction being assumed to be of the first order with respect to the aromatic compound, the experimental initial rates found with the more dilute solution were multiplied by the required factor, and the rates thus calculated were included in the plots (cf. Fig. 1). The calculated rates were found to fall well on the lines, confirming the first order which had been anticipated from the results of early work on sulphonations (Martinsen, *Z. physikal. Chem.*, 1908, **62**, 713).

(c) *Activation energies.* From the velocity constants at different temperatures the activation energies were calculated by the Arrhenius equation. Since, in the present work, most reactions were studied at two temperatures only, the corresponding activation energies (see Table II) represent only approximate values.

Discussion.

The second order of the sulphonation reaction with respect to sulphur trioxide is found to be a common feature of the eight reactions so far investigated by this method. If from this result we conclude that two single sulphur trioxide molecules are required for reaction, then the function of the second molecule can no longer be attributed to some physical interaction with the substituent. Such interaction, if of a dipolar nature, might have explained the behaviour of nitro- and halogeno-compounds, but the hypothesis must be discarded in view of the second order found for the sulphonation of unsubstituted benzene. Alternatively, the second trioxide molecule might act as a basic catalyst temporarily accepting a proton, the removal of which facilitates the approach of the attacking trioxide molecule. Although there is no definite evidence against such a mechanism, it now seems equally likely that the dimeric form, S_2O_6, is the active species of sulphur trioxide. If the dimer is supposed to exist in equilibrium, in small amounts, with two monomeric molecules, then the

Fig. 2.

Initial rates for α-nitronaphthalene at 40°.

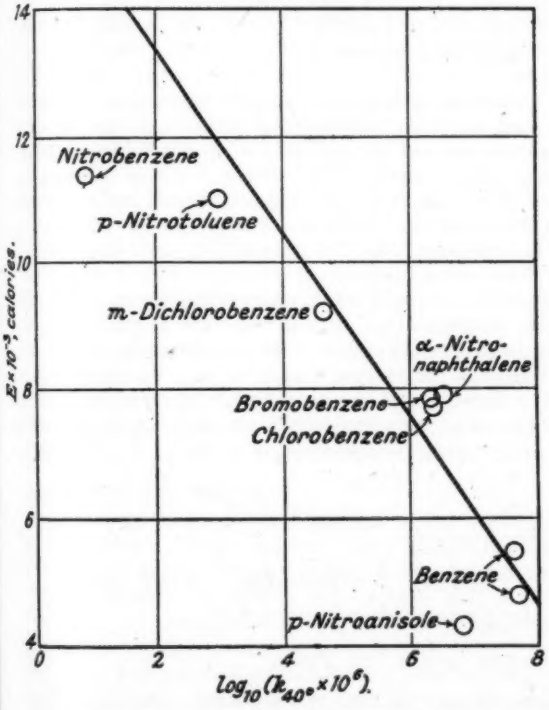
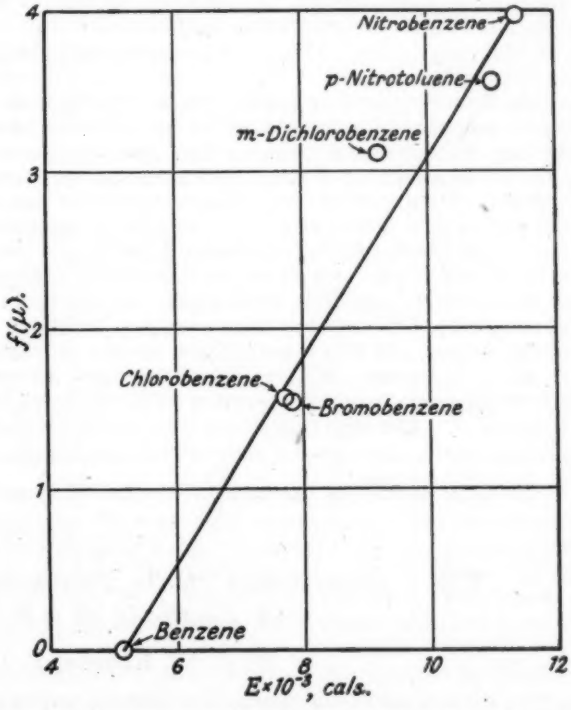


Fig. 3.

Dipole moment functions and activation energies.



rate of sulphonation would be proportional to the square of the sulphur trioxide concentration. In this connection, it is noteworthy that Michael and Weiner (*J. Amer. Chem. Soc.*, 1936, **58**, 294) have already suggested that S_2O_6 is the active sulphonating agent in the action of sulphur trioxide on the olefins. Although the information at present available is still insufficient to settle conclusively the detailed mechanism of substitution by sulphur trioxide, the scheme

$$2SO_3 \rightleftharpoons S_2O_6;\ ArH + S_2O_6 \longrightarrow Ar{\cdot}S_2O_6H;\ Ar{\cdot}S_2O_6H \rightleftharpoons Ar{\cdot}SO_3H + SO_3$$

would explain the second order with respect to SO_3, the first order with respect to ArH, and the retardation by the product.

With regard to the specific influence of substituents on the reactivity of the nucleus, some tentative conclusions may now be drawn. In Fig. 2 the logarithms of the velocity constants, k, at 40°, which were made comparable by dividing the observed constants, k', by the molar concentration of the aromatic reagent, have been plotted against the activation energies. If the effects of substituents on the rate of sulphonation were entirely accounted for by the differences of the activation energies of the substituted compounds from that of benzene, then the points should fall on a straight line, drawn through the value for benzene, with a slope of $-2{\cdot}303\boldsymbol{RT}$. A line of the theoretical slope has been drawn through the mean of the two values available for benzene, and it is seen that, except for nitrobenzene and *p*-nitroanisole, this relation is roughly obeyed. From this line an average value of 5·24 can be deduced for the $\log_{10} PZ$ factor of the sulphonations.

The fact that nitrobenzene does not fall on the line is not surprising, since the measured velocity constant was divided by the total molar concentration of the medium, but *p*-nitroanisole probably represents a truly anomalous case, though the activation energy for this compound should be confirmed by further measurements. It is, however, of interest to find that the three halogen derivatives conform with the relation between rate and activation energy, and that α-nitronaphthalene behaves as a substituted benzene in this case. The change of activation energy in the series: benzene 5,200 cals., chlorobenzene 7,700 cals., *m*-dichlorobenzene 9,200 cals., is also noteworthy.

TABLE II.

Velocity constants, activation energies, and dipole-moment functions.

Compound.	$k_{40°}$ (l./g.-mol. sec.).	E (cals./g.-mol.).	f(μ).
Benzene	48·8	4,800	0·00
*Benzene (Paneth)	40·8	5,500	0·00
*Chlorobenzene	2·40	7,720	1·56
Bromobenzene	2·10	7,840	1·53
m-Dichlorobenzene	$4·36 \times 10^{-2}$	9,220	3·12
*Nitrobenzene	$7·85 \times 10^{-6}$	11,400	3·97
**p*-Nitrotoluene	$9·53 \times 10^{-4}$	11,025	3·56
p-Nitroanisole	6·29	4,320	5·13
α-Nitronaphthalene	3·27	7,900	—

* Indicates results obtained by previous workers.

In order to correlate further the kinetic and electronic aspects of aromatic substitution, a function of dipole moments of monosubstituted benzenes has been used as a rough measure of changes in the electronic density of the benzene nucleus. This function f(μ) is plotted against the activation energy in Fig. 3, and in spite of the difficulty of the experimental measurements a definite connection between f(μ) and changes in E appears. *p*-Nitroanisole, which again represents the only exception to the general relation, is not included in the plot in view of the known peculiar effect of methoxyl groups on the dipole moments of benzene derivatives. For the monosubstituted compounds f(μ) is simply the dipole moment, but for the disubstituted compounds it is the algebraic sum of the two group moments. Moments are given positive signs for electronic displacements in the direction away from the nucleus. It thus appears that in general for this series of compounds, the effect of substituents on the activation energy is correlated with changes of electron density at the point of attack of the reagent, and that these changes are of a permanent nature, as is evident from the corresponding changes in dipole moments. With certain substituent groups, perhaps for instance with ·OCH_3, the time-variable effects may well come into operation on the approach of the reagent, and this would probably give an abnormal value for P. Although it is too early to generalise about the effects of substituents, we may conclude from the present results that halogen does not fall into the class which brings about changes in the probability factor.

PHYSICAL CHEMISTRY LABORATORY, OXFORD UNIVERSITY. [*Received, October 3rd*, 1944.]

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178. *Experiments on the Synthesis of Purine Nucleosides. Part IX. A Synthesis of* 9-d-*Xylopyranosidoadenine.*

By G. W. KENNER, B. LYTHGOE, and A. R. TODD.

Condensation of 4 : 6-diaminopyrimidine with *d*-xylose appears to give two glycosidic products. The first, obtained in low yield, is a crystalline 6-*amino*-4-d-*xylosidaminopyrimidine*, and the second and major product is an intractable syrup. Coupled with diazotised 2 : 5-dichloroaniline, these products give two isomeric azo-xylosides, each giving a distinct crystalline triacetyl derivative. Reductive fission of the azo-linkage in each of these isomeric triacetates gives one and the same 5 : 6-*diamino*-4-*triacetyl*-d-*xylosidaminopyrimidine*. The significance of this remarkable sequence of reactions is discussed.

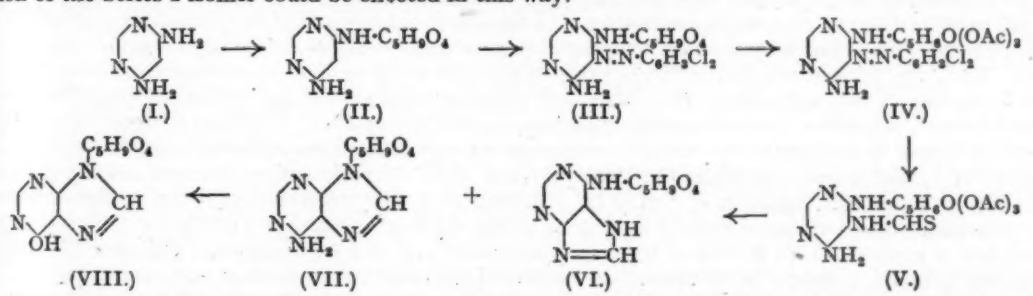
Thioformylation of 5 : 6-diamino-4-triacetyl-*d*-xylosidaminopyrimidine, followed by cyclisation and deacetylation, gives a mixture of 9-d-*xylopyranosidoadenine* and 6-d-*xylosidaminopurine*. The former is readily deaminated to 9-d-*xylopyranosidohypoxanthine* and is shown to be a pyranoside by periodate oxidation.

FOLLOWING the discovery of a convenient method for the preparation of 4 : 6-diaminopyrimidine (Part IV; Kenner, Lythgoe, Todd, and Topham, J., 1943, 574), it was decided to proceed to the synthesis of 9-*d*-xylosidoadenine, using a route analogous to that described for 9-*d*-xylopyranosido-2-methyladenine (Part VI; Baddiley, Lythgoe, and Todd, this vol., p. 318). In undertaking this synthesis we had two objects in view, first to establish a route to the ribosides of adenine (including adenosine) on the closest analogous case, using the more readily available *d*-xylose as sugar component, and second to extend our range of synthetic purine *d*-xylosides in order to examine a series of these compounds bearing a variety of substituents in the purine nucleus.

Condensation of 4 : 6-diaminopyrimidine (I) with *d*-xylose under conditions similar to those used in the analogous condensation of 4 : 6-diamino-2-methylpyrimidine (Part III; Baddiley, Lythgoe, and Todd, J., 1943, 571) gave in low yield (*ca.* 10%) a crystalline glycoside which we designate 6-*amino*-4-d-*xylosidaminopyrimidine-I* (II), together with a considerably larger amount of resinous glycosidic material which could not

be crystallised. Despite an extended series of experiments we were unable to determine reaction conditions leading with certainty to an increased, or even constant, yield of crystalline material. A rather similar case had already been encountered in the preparation of 6-amino-4-*d*-xylosidamino-2-methylthiopyrimidine. There it was known that the resinous fraction of the crude xyloside contained considerable quantities of crystalline material (Part III, *loc. cit.*) as well as an isomeric xyloside (unpublished observations; cf. Baddiley, Kenner, Lythgoe, McNeil, Todd, and Topham, *Chem. Ind.*, 1943, **62**, 433). The possibility that the same might hold for the resinous glycosidic product from 4 : 6-diaminopyrimidine had therefore to be borne in mind.

The crystalline 6-amino-4-*d*-xylosidaminopyrimidine-I coupled readily with diazotised 2 : 5-dichloroaniline, giving 6-*amino*-4-d-*xylosidamino*-5-(2′ : 5′-*dichlorobenzeneazo*)*pyrimidine-I* (III), m. p. 166°. When the same coupling procedure was applied to the resinous material remaining after the crystalline xyloside had been separated from the xylosidisation mixture, a product was obtained which, after several recrystallisations, gave an isomeric 6-*amino*-4-d-*xylosidamino*-5-(2′ : 5′-*dichlorobenzeneazo*)*pyrimidine-II* (III), m. p. 250°. It thus seemed probable that the condensation of 4 : 6-diaminopyrimidine with *d*-xylose had given rise to two isomeric *d*-xylosides, and that in carrying out the projected nucleoside synthesis two series of isomeric intermediates and final products might be expected. For convenience we describe them for the present as Series I and Series II, the individual members being distinguished by adding to their systematic names the suffix I or II. The synthetic route to the purine glycosides employed in both series was similar to that used in Part VI (*loc. cit.*). Acetylation of the azo-compounds (III) before reduction was adopted, since preliminary experiments in Series I showed that reductive fission of (III), followed by thioformylation, gave a product difficult to isolate in a pure state. It was found by experience that the only satisfactory way to separate Series I from Series II was by direct crystallisation of the 6-amino-4-*d*-xylosidaminopyrimidine-I from the crude condensation product of *d*-xylose and 4 : 6-diaminopyrimidine; the resinous residue then consisted mainly of the Series II isomer. In the hope of simplifying the separation several experiments were carried out in which the crude xylosidisation product was coupled with diazotised 2 : 5-dichloroaniline, and the product acetylated and submitted to chromatographic analysis; possibly owing to the preponderance of the Series II compound in the mixture, no ready isolation of the Series I isomer could be effected in this way.



Because of the greater availability of the starting material the nucleoside synthesis was first carried out from 6-amino-4-*d*-xylosidamino-5-(2′ : 5′-dichlorobenzeneazo)pyrimidine-II. Treatment with acetic anhydride in pyridine solution yielded 6-*amino*-4-*triacetyl*-d-*xylosidamino*-5-(2′ : 5′-*dichlorobenzeneazo*)*pyrimidine-II* (IV), which was reduced smoothly with Raney nickel and hydrogen to 5 : 6-*diamino*-4-*triacetyl*-d-*xylosidamino*-*pyrimidine*. (The Series II suffix is omitted from this intermediate and from the products obtained from it for reasons which will be made clear later.)

6-*Amino*-4-*triacetyl*-d-*xylosidamino*-5-*thioformamidopyrimidine* (V), prepared from this diamine by heating with dithioformic acid, was cyclised by heating in pyridine solution. The mixture of acetylated purine xylosides thus obtained did not crystallise readily and was accordingly deacetylated; from the product, two crystalline *d*-xylosides were isolated. One of these was evidently 9-d-*xylosidoadenine* (VII), since it could be hydrolysed to adenine and *d*-xylose, was insoluble in alkali, and was readily deaminated to 9-d-*xylosidohypoxanthine* (VIII). The other also yielded adenine and *d*-xylose on hydrolysis, but was readily soluble in alkali. From this and by analogy with the analogous 2-methyladenine xylosides (Part VI, *loc. cit.*) we regard this substance as 6-d-*xylosidaminopurine* (VI).

The size of the lactol ring in (VII) was determined by periodate titration by the method described in Part VIII (Lythgoe and Todd, this vol., p. 592). The xyloside reacted with 2 mols. of the reagent, liberating 1 mol. of formic acid; it is therefore more accurately described as 9-d-*xylopyranosidoadenine* and it would follow that (VIII) and presumably (V) also are *d*-xylopyranosides. 9-*d*-Xylopyranosidoadenine is very similar in ease of hydrolysis and optical rotation to 9-*d*-xylopyranosido-2-methyladenine (Part VI, *loc. cit.*), suggesting that both have the same stereochemical configuration; its absorption spectrum is, as anticipated, closely similar to that of adenosine.

The same synthetic scheme was now applied to the less accessible 6-amino-4-*d*-xylosidamino-5-(2′ : 5′-dichlorobenzeneazo)pyrimidine-I in the expectation that a second pair of adenine xylosides would be obtained isomeric with those above described. 6-*Amino*-4-*triacetyl*-d-*xylosidamino*-5-(2′ : 5′-*dichlorobenzeneazo*)*pyrimidine-I* was readily obtained and the series of reactions used in the case of the Series II compound was applied. In this case the hydrogenation product was in the first experiment thioformylated without isolation, and owing

to the small amount available the thioformamido-compound (V) was not purified before cyclisation. Only one crystalline purine xyloside was isolated, probably owing to the use of impure thioformamido-compound; we had already observed in work on Series II that unless the pure thioformamido-compound were used crystallisation of the 6-*d*-xylosidaminopurine was barely possible. The crystalline product, although of slightly higher m. p. (298°) than the 9-*d*-xylosidoadenine (m. p. 292°) obtained from the Series II azo-glycoside, was otherwise identical in properties and a mixed m. p. showed no definite depression. Further evidence of identity was obtained by periodate titration, which showed the xyloside to have a pyranoside structure and to give a scission product with this reagent whose optical rotation was identical with that of the scission product of the Series II compound. Had the xylosides obtained in the two series been respectively α- and β-glycosides, the scission products would have been enantiomorphous (cf. Part VIII, *loc. cit.*). Finally, specimens of the two products were submitted to *X*-ray examination by Dr. I. G. Edmunds of the Manchester College of Technology; to him we are deeply indebted. Careful comparison of their *X*-ray powder photographs, which showed a large number of reflections, confirmed that the two materials were identical.

The identity of the 9-*d*-xylosidoadenine from the two isomeric azo-glycosides being established, the reduction of 6-amino-4-triacetyl-*d*-xylosidamino-5-(2′ : 5′-dichlorobenzeneazo)pyrimidine-I with Raney nickel and hydrogen was repeated and this time the hydrogenation product was isolated before thioformylation. It proved to be identical (mixed m. p. and, within the limits of experimental error, optical rotation) with 5 : 6-diamino-4-triacetyl-*d*-xylosidaminopyrimidine already obtained by similar hydrogenation of 6-amino-4-triacetyl-*d*-xylosidamino-5-(2′ : 5′-dichlorobenzeneazo)pyrimidine-II. Evidently the two series become one during the hydrogenation process.

What, then, is the nature of the isomerism shown by the azoglycosides of Series I and Series II? On the evidence so far presented and in view of our failure to isolate two crystalline homogeneous xylosides from the reaction between 4 : 6-diaminopyrimidine and *d*-xylose, it might be suggested that the two azo-glycosides are simply *cis*- and *trans*-azo-compounds. This seems most improbable, since coupling conditions are the same in their formation and since acid hydrolysis of both the Series I and the Series II compound yields one and the same 4 : 6-*diamino*-5-(2′ : 5′-*dichlorobenzeneazo*)*pyrimidine*, and we conclude that isomers belonging to the two series are produced in the original xylosidisation. Although it is known that in some cases pyrimidine rings can be opened to give isomeric open-chain compounds [*e.g.*, acetylation of 4-amino-5-cyanopyrimidine (Part II; J., 1943, 386)], the subsequent course of reactions in the two series seems to preclude this being the reason for the formation of two xylosides. The conclusion seems inevitable that the isomerism concerns the sugar residue, *i.e.*, that they are α- and β-xylosides or furanoside and pyranoside. Evidence to decide between these alternatives should be obtainable by periodate oxidation, assuming that this method of attack can be extended to the case of xylosidaminopyrimidines (cf. Part VIII, *loc. cit.*). Experiments to this end are in progress and will shortly be reported. Meanwhile it may be observed that the procedure used for condensing 4 : 6-diaminopyrimidine with *d*-xylose is strictly analogous to the classical method of Fischer for the preparation of *O*-glycosides, a method which is known to yield a mixture of α- and β-glycosides. Whether the difference between our isomeric xylosides be of the α–β or furanose–pyranose type, it is clear that rearrangement of one isomer must occur during hydrogenation in ethyl acetate solution with a Raney nickel catalyst. As far as we are aware, no rearrangement of either type under such conditions has so far been described in the literature, and, if established, the observation might lead to developments of some significance in the chemistry of *N*-glycosides in general.

A feature of interest in the synthesis of the xylosides of adenine and 2-methyladenine (Part VI, *loc. cit.*) is the simultaneous production of acetylated 9-xylosido- and 6-xylosidamino-purines, cyclisation of the appropriate thioformamido-compounds proceeding in two directions. This was unexpected, since we had assumed by analogy with the behaviour of 6-amino-4-methylamino-5-thioformamido-2-methylthiopyrimidine (Part I; Baddiley, Lythgoe, McNeil, and Todd, J., 1943, 383) that the cyclisation would lead exclusively to the 9-substituted purine. It is impossible on present evidence to give a precise explanation of this apparent anomaly. It might be argued that substitution of a sugar residue for the 4-amino-group in the pyrimidine is not strictly analogous to substitution of an alkyl group or that steric hindrance makes ring closure in the desired direction more difficult. Another possibility is that production of the 6- and the 9-substituted purines is bound up with the fact that in the cases examined so far the sugar residue has been acetylated. In such cases one cannot exclude the possibility of chelation involving the glycosidic NH group and the carbonyl of the acetyl residue at C_2 in the sugar chain. The effect of such chelation would be indirectly to increase the electron density at the nitrogen atom in the imino-group at C_6, so enabling that group to take part in the cyclisation process.

Experimental.

The activated aluminium oxide used in these experiments was prepared by heating "alumina hydrate" (British Aluminium Co. Ltd.) from room temperature to 360° during 5 hours.

Condensation of 4 : 6-*Diaminopyrimidine with* d-*Xylose*.—To 4 : 6-diaminopyrimidine (40 g.) and *d*-xylose (20 g.) in absolute alcohol (1 l.), saturated alcoholic hydrogen chloride (8 c.c.) was added, and the mixture refluxed for a total of 22 hours spread over 3 successive days. Dry benzene was added at intervals during the operation, and water removed azeotropically through a 50 cm. Fenske column with a total reflux variable take-off head. The resulting solution was passed through a column of activated alumina (1600 g.), and the column was washed with absolute alcohol (8 l.) until no more 4 : 6-diaminopyrimidine came through. Elution of the column was effected by washing with water (9 l.) until the washings gave only a faint Molisch reaction, and the eluate was evaporated under reduced pressure at 30° to small

bulk (*ca.* 100 c.c.) and set aside overnight. 6-*Amino*-4-d-*xylosidaminopyrimidine-I* (*ca.* 3·5 g.) separated in colourless prisms; recrystallised from water, it had m. p. 207° (decomp.) and $[\alpha]_D^{19°}$ + 154° (*c*, 0·12 in water) (Found in material dried at 100°: C, 44·7; H, 6·0; N, 23·5. $C_9H_{14}O_4N_4$ requires C, 44·6; H, 5·8; N, 23·2%).

Hydrolysis. The xyloside (0·25 g.) was refluxed for 30 mins. with N/10-hydrochloric acid (15 c.c.). The resulting solution was made up to 20 c.c. and divided into 2 equal portions (*a*) and (*b*). (*a*) When saturated aqueous picric acid (10 c.c.) was added, 4 : 6-diaminopyrimidine picrate (0·15 g.) separated; recrystallised from water, it had m. p. 297° (decomp.), undepressed by an authentic specimen. (*b*) A solution of phenylhydrazine in aqueous acetic acid was added, and the mixture heated in a boiling water-bath. After 18 mins. *d*-xylosazone began to separate; it had m. p. 163°, undepressed in admixture with a specimen prepared under precisely similar conditions from authentic *d*-xylose.

The aqueous mother-liquors left after separation of 6-amino-4-*d*-xylosidaminopyrimidine-I gave on further concentration only a brownish resin, which would not crystallise and served as starting material for compounds of Series II.

Series II.

6-*Amino*-4-d-*xylosidamino*-5-(2′ : 5′-*dichlorobenzeneazo*)*pyrimidine-II.*—2 : 5-Dichloroaniline (32·4 g.), dissolved in dilute hydrochloric acid (200 c.c. of concentrated acid + 1 l. of water), was diazotised in the usual way. The diazo-solution, neutralised with excess of sodium bicarbonate, was added to the aqueous mother-liquor remaining after the separation of the crystalline 6-amino-4-*d*-xylosidaminopyrimidine-I (prepared from 40 g. of 4 : 6-diaminopyrimidine as described above). After standing overnight, the yellow solid was collected, washed with water, dried, ground up with ether to remove impurities, and again dried. (Yield, 28 g.) The *azo-glycoside*, recrystallised from pyridine–alcohol, formed orange-yellow plates, m. p. 250° (decomp.). Dried at 100°/0·5 mm., the crystals still contained pyridine (Found in material dried at 140°/0·5 mm.: C, 43·6; H, 4·3; N, 20·3. $C_{15}H_{16}O_4N_6Cl_2$ requires C, 43·4; H, 3·9; N, 20·2%). It showed $[\alpha]^{20°}$ + 11° (*c*, 0·24 in pyridine; Wratten No. 29 light filter).

6-*Amino*-4-*triacetyl*-d-*xylosidamino*-5-(2′ : 5′-*dichlorobenzeneazo*)*pyrimidine-II.*—*Method* 1. The above crude azo-glycoside (28 g.) was kept overnight with acetic anhydride (150 c.c.) in pyridine (500 c.c.). Alcohol (200 c.c.) was added cautiously and after 2 hours the solution was evaporated, and the residue taken up in ethyl acetate and passed through a column (40 cm. × 6 cm.) of activated alumina. When the column was washed with ethyl acetate, the bulk of the material was eluted as a uniform yellow band. The eluate was evaporated, and the residue recrystallised from benzene, giving yellow needles, m. p. 138—139° (Found in material dried at 100°: C, 46·3; H, 4·3; N, 15·5. $C_{21}H_{22}O_7N_6Cl_2$ requires C, 46·6; H, 4·1; N, 15·5%). Yield, 8 g. (11% calculated on original *d*-xylose used). $[\alpha]^{19°}$ − 306° (*c*, 0·37 in chloroform; Wratten No. 29 light filter).

Method 2. 4 : 6-Diaminopyrimidine (2·2 g.; 1 mol.) was condensed with *d*-xylose (3·0 g.; 1 mol.) in the normal manner (see above), refluxing being continued for 60 hours. The resulting alcoholic solution was evaporated in a vacuum, and the residue dissolved in water and coupled with diazotised 2 : 5-dichloroaniline (from 3·5 g. of the amine) in presence of excess of sodium bicarbonate. The precipitate of mixed azo-compounds (3·25 g.) was collected, dried, and acetylated at room temperature with acetic anhydride (15 c.c.) in pyridine (75 c.c.). The crude acetylated material was dissolved in ethyl acetate and passed through a column of activated aluminium oxide (30 × 2·5 cm.). On development with ethyl acetate three distinct bands were visible, an upper dark band containing much tarry material, a middle yellow band of sugar-free azopyrimidine derivative, and a lower yellow band of acetylated azo-glycosides. The lower yellow band was eluted with ethyl acetate, the eluate evaporated, and the residue recrystallised from benzene. 6-Amino-4-triacetyl-*d*-xylosidamino-5-(2′ : 5′-dichlorobenzeneazo)pyrimidine-II was obtained in yellow needles, m. p. 138—139°, undepressed in admixture with the product obtained by Method 1 above (yield, 0·56 g.; 5·2% calculated on *d*-xylose). A sample, dissolved in chloroform and hydrolysed by addition of methanolic sodium methoxide (1 atom of sodium) and leaving overnight, gave orange-yellow plates of 6-amino-4-*d*-xylosidamino-5-(2′ : 5′-dichlorobenzeneazo)pyrimidine-II, m. p. and mixed m. p. 249—250° (decomp.).

5 : 6-*Diamino*-4-*triacetyl*-d-*xylosidaminopyrimidine.*—The above acetyl-azo-compound (8 g.) was hydrogenated in ethyl acetate (100 c.c.) at 80°/100 atms. for 7 hours, a Raney nickel catalyst being used. The product which separated on cooling was dissolved in alcohol, and the solution filtered from nickel and evaporated. Trituration with light petroleum, followed by recrystallisation from ethyl acetate–alcohol, gave colourless needles (5·3 g.; 93%), m. p. 200°, $[\alpha]_D^{20°}$ + 6° (± 4°) (*c*, 0·34 in chloroform) (Found: C, 46·8; H, 5·6; N, 17·7. $C_{15}H_{21}O_7N_5$ requires C, 47·0; H, 5·5; N, 18·3%).

6-*Amino*-4-*triacetyl*-d-*xylosidamino*-5-*thioformamidopyrimidine.*—5 : 6-Diamino-4-triacetyl-*d*-xylosidaminopyrimidine-II (4 g.) was refluxed for 3 hours in alcohol (100 c.c.) with dithioformic acid (from 36 g. of the sodium salt). A second equal amount of dithioformic acid was added, heating continued for 3 hours, and the mixture left overnight. The liquid was filtered, the residue washed with hot alcohol, and the combined filtrate and washings evaporated to small bulk (30 c.c.). The *thioformyl* derivative which separated was recrystallised from alcohol, forming rosettes of colourless needles (1·8 g.; 40%), m. p. 187° (decomp.), which appeared to be hydrated (Found: C, 42·8; H, 5·2; N, 15·9. $C_{16}H_{21}O_7N_5S,H_2O$ requires C, 43·2; H, 5·2; N, 15·7%). Resinous material which remained in the mother-liquors could be used successfully for the preparation of 9-*d*-xylopyranosidoadenine.

9-d-*Xylopyranosidoadenine and* 6-d-*Xylosidaminopurine.*—The above thioformyl compound (1·5 g.) was refluxed in pyridine (10 c.c.) in a slow stream of nitrogen for 16 hours, by which time evolution of hydrogen sulphide had ceased. Solvent was removed in a vacuum, and the residue dissolved in dry chloroform (20 c.c.) and, after addition of methanolic sodium methoxide (0·08 g. of sodium in 20 c.c. of methanol), kept overnight. The solution was now evaporated in a vacuum, chloroform (20 c.c.) added, and the precipitate collected and dissolved in hot water (10 c.c.). On cooling, a crystalline solid (0·14 g.) (A) separated, leaving an alkaline mother-liquor (B).

(A) Recrystallisation from water gave 9-d-*xylopyranosidoadenine* in colourless plates, m. p. 292° (decomp.) (Found in material dried at 140°: C, 44·8; H, 5·0; N, 26·2. $C_{10}H_{13}O_4N_5$ requires C, 45·0; H, 4·9; N, 26·2%). The substance had $[\alpha]_D^{18°}$ − 26° (*c*, 0·28 in water) and its absorption spectrum showed a maximum at 2585 A. (ε, 15,000) in N/20-hydrochloric acid and at 2605 A. (ε, 12,400) in N/20-sodium hydroxide.

Periodate titration. Amount used, 0·094 g. Mols. of sodium periodate used per mol. of xyloside, 2·00; mol. of formic acid liberated per mol. of xyloside, 0·93. Rotation of final solution + 0·08° (*c*, 0·094; *l* = 2 dcm.).

Hydrolysis. The xyloside (50 mg.) (unaffected by boiling with N/10-sulphuric acid for 1 hour) was heated for 5 hours with N-acid (5 c.c.) and then exactly neutralised with sodium hydroxide. The solution was evaporated, and the residue extracted with alcohol. The undissolved material, dissolved in water and treated with picric acid, gave adenine picrate, m. p. and mixed m. p. 294—295°. The alcoholic extract was evaporated to dryness, and the product heated with acetic anhydride (2 c.c.) and fused sodium acetate (20 mg.) for 1 hour at 100°. On working up in the usual way, β-tetra-acetyl-*d*-xylose was obtained, m. p. and mixed m. p. 125—126°.

(B) The mother-liquors and washings from (A) were exactly neutralised with hydrochloric acid and evaporated in a vacuum. The residue was recrystallised from water. 6-d-*Xylosidaminopurine* was obtained in colourless needles (0·12 g.), m. p. 219° (decomp.) (Found in material dried at 140°: C, 44·8; H, 4·8; N, 25·9. $C_{10}H_{13}O_4N_5$ requires C, 45·0; H, 4·9; N, 26·2%). $[\alpha]_D^{22°}$ − 7° (*c*, 0·14 in water). Hydrolysis was readily effected with N/10-hydrochloric acid

and in the hydrolysis solution adenine and *d*-xylose were identified in the usual way as adenine picrate, m. p. 294—295°, and β-tetra-acetyl *d*-xylose, m. p. 124—125°.

9-d-*Xylopyranosidohypoxanthine.*—9-*d*-Xylopyranosidoadenine (0·1 g.) was dissolved in hot water (10 c.c.) and cooled to 65°, and sodium nitrite (0·257 g.; 10 mols.) added, followed by N-hydrochloric acid (5 c.c.). The temperature was maintained at 65° and evolution of nitrogen ceased in 30 mins.; the solution was then exactly neutralised with sodium hydroxide and concentrated. As no crystalline material had separated after 3 days, the solution was evaporated to dryness, and the residue kept overnight with acetic anhydride (1·5 c.c.) in pyridine (3·5 c.c.). The solution was evaporated in a vacuum, the residue thoroughly extracted with boiling chloroform (15 c.c. in all), and the chloroform evaporated, giving the acetylated material in the form of a resin. This product was dissolved in saturated methanolic ammonia (15 c.c.), and the solution set aside for 2 days and evaporated in a vacuum. On recrystallisation of the residue from methanol 9-d-*xylopyranosidohypoxanthine* was obtained in colourless prisms (10 mg.), m. p. 222°; the crystals appeared to be hydrated and held their water of crystallisation tenaciously even on heating at 140° for 5 hours (Found: C, 41·9; H, 5·1; N, 19·6. $C_{10}H_{12}O_5N_4,H_2O$ requires C, 42·0; H, 4·9; N, 19·6%).

Series I.

6-*Amino*-4-d-*xylosidamino*-5-(2′ : 5′-*dichlorobenzeneazo*)*pyrimidine-I.*—2 : 5-Dichloroaniline (0·4 g.) was dissolved in boiling water (12 c.c.), concentrated hydrochloric acid (2·5 c.c.) added, and the solution cooled to 0° and diazotised with sodium nitrite (0·18 g.). The filtered diazo-solution was added to a suspension of powdered 6-amino-4-*d*-xylosidaminopyrimidine-I (0·6 g.) in a little water, and excess of sodium bicarbonate (2·5 g. in 30 c.c. of water) added at once. After 3 hours the solid product was collected, dried, and recrystallised from pyridine–alcohol. The *azo*-compound (0·58 g.; 56%) formed clusters of yellow needles, m. p. 166° (decomp.), which appeared to be hydrated (Found in material dried at 75°: C, 41·0; H, 4·8; N, 19·2; loss at 100°, 6·1. $C_{15}H_{16}O_4N_6Cl_2,1\frac{1}{2}H_2O$ requires C, 40·8; H, 4·3; N, 19·0; H_2O, 6·1%). A Wratten No. 29 filter and a source of white light being used, it had $[\alpha]^{20°}$ — 19° (*c*, 0·24 in pyridine).

6-*Amino*-4-*triacetyl*-d-*xylosidamino*-5-(2′ : 5′-*dichlorobenzeneazo*)*pyrimidine-I.*—The above azo-compound (4·0 g.) was kept overnight with acetic anhydride (20 c.c.) in pyridine (100 c.c.). Alcohol (20 c.c.) was now added and after 3 hours the solution was evaporated. The residue crystallised from benzene or ethyl acetate–alcohol in yellow needles (2·05 g.; 38%), m. p. 219—220° (Found in material dried at 100°: C, 46·1; H, 4·1; N, 15·5. $C_{21}H_{22}O_7N_6Cl_2$ requires C, 46·6; H, 4·1; N, 15·5%). With white light and a Wratten No. 29 filter it showed $[\alpha]^{19°}$ + 21° (*c*, 0·24 in chloroform).

5 : 6-*Diamino*-4-*triacetyl*-d-*xylosidaminopyrimidine.*—The above triacetyl-azo-compound (1·8 g.) in ethyl acetate (100 c.c.) was hydrogenated under pressure (80 atm.) at 100° for 4 hours, a Raney nickel catalyst being used. The catalyst was filtered off and washed with alcohol, and the combined filtrate and washings evaporated. The residue crystallised on trituration with light petroleum and was used directly for the next stage. In a second experiment it was recrystallised from ethyl acetate–alcohol and then had m. p. 198°, undepressed in admixture with the diamine prepared from the Series II azo-glycoside. It had $[\alpha]_D^{18°}$ + 10° (± 7°) (*c*, 0·17 in chloroform).

9-d-*Xylopyranosidoadenine.*—To the above crude diamine, dissolved in hot alcohol (100 c.c.), dithioformic acid (from 12 g. of the hydrated sodium salt) was added, and the mixture refluxed for 2 hours. A second similar quantity of dithioformic acid was now added, refluxing continued for a further 2 hours, and the whole kept overnight. The mixture was now heated to boiling, filtered, and the residue of dithioformic acid washed thoroughly with boiling alcohol (300 c.c.). Filtrate and washings were evaporated under reduced pressure, giving a crude resinous thioformyl-compound which did not crystallise readily and was not further purified.

The crude thioformyl derivative was freed from alcohol by heating at 100°/0·5 mm. for 4 hours, then refluxed in dry pyridine (10 c.c.) in a stream of nitrogen; after 16 hours evolution of hydrogen sulphide had ceased. The solution was evaporated under reduced pressure, but the residue could not be crystallised directly. It was accordingly dissolved in dry chloroform (25 c.c.) and after addition of a solution of sodium methoxide (0·1 g. of sodium in 25 c.c. of methanol) kept overnight. The resulting solution was evaporated in a vacuum, and the brownish residue recrystallised twice from water (charcoal). 9-d-*Xylopyranosidoadenine* was obtained in colourless prisms, m. p. 298° (decomp.) (Found in material dried at 140°/0·5 mm.: C, 45·2; H, 5·1; N, 26·0. $C_{10}H_{13}O_4N_5$ requires C, 45·0; H, 4·9; N, 26·2%). Yield of pure material, 82 mg. The solubility of the substance in water was not increased by adding alkali. *Light absorption.* (*a*) In N/20-hydrochloric acid: maximum at 2590 A. (ε, 13,000). (*b*) In N/20-sodium hydroxide: maximum at 2605 A. (ε, 14,000).

Periodate titration. Amount of xyloside used 0·0515 g. Periodate absorbed, 1·96 mols./mol.; formic acid liberated, 0·99 mol./mol. Rotation of final solution + 0·08° (*c*, 0·103; *l* = 2 dcm.)

The mother-liquors from the crystallisation of the 9-*d*-xylopyranosidoadenine-I were carefully neutralised with hydrochloric acid (N/10); only gummy material separated and no crystalline 6-xylosidaminopurine could be isolated from it.

4 : 6-*Diamino*-5-(2′ - 5′-*dichlorobenzeneazo*)*pyrimidine*, prepared in 90% yield by coupling 4 : 6-diaminopyrimidine with diazotised 2 : 5-dichloroaniline in presence of sodium hydrogen carbonate in the usual manner, formed yellow needles from pyridine, m. p. 281° (Found in material dried at 140°: N, 29·2. $C_{10}H_8N_6Cl_2$ requires N, 29·7%).

Hydrolysis of the Isomeric 6-*Amino*-4-d-*xylosidamino*-5-(2′ : 5′-*dichlorobenzeneazo*)*pyrimidines.*—The following procedure was applied in each case: The glycoside (30 mg.) was refluxed in a mixture of alcohol (3 c.c.) and N-sulphuric acid (5 c.c.) for 3 hours, and the solution cooled, neutralised with N-sodium hydroxide (5 c.c.), and evaporated. Water was added, and the yellow solid collected, dissolved in hot alcohol (5 c.c.), and purified by passing through a column of activated alumina, washing with alcohol being continued till the yellow band was eluted. The alcoholic washings were concentrated, and the azopyrimidine allowed to crystallise. The Series I isomer gave a product, m. p. 278—279°, undepressed in admixture with authentic 4 : 6-diamino-5-(2′ : 5′-dichlorobenzeneazo)pyrimidine (m. p. 278°). The Series II glycoside gave a product, m. p. 277—278°, undepressed by an authentic specimen or by the product from the Series I isomer.

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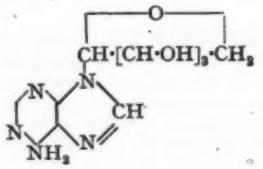
179. *Experiments on the Synthesis of Purine Nucleosides. Part X. A Synthesis of* 9-d-*Ribopyranosidoadenine.*

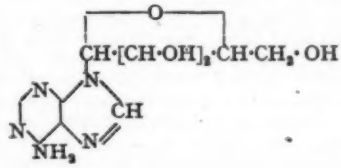
By J. Baddiley, G. W. Kenner, B. Lythgoe, and A. R. Todd.

A synthesis of 9-d-*ribopyranosidoadenine* by a method analogous to that used for the corresponding *d*-xyloside (Part IX, preceding paper) is described. The product resembles adenosine (II) but is more resistant to hydrolysis. A point of interest in the synthesis is the absence of evidence of formation of isomeric glycosides from 4 : 6-diaminopyrimidine and *d*-ribose.

In previous papers of this series (Part VI, this vol., p. 318; Part IX, preceding paper) we have described syntheses of two 9-*d*-xylosidopurines, using a general method starting from 6-amino-4-*d*-xylosidaminopyrimidines prepared by direct condensation of *d*-xylose with appropriate 4 : 6-diaminopyrimidines. The successful completion of these syntheses led us naturally to attempt the synthesis of 9-*d*-ribosidoadenine by this method and the present communication records the results obtained. The fact that the purine xylosides so far prepared are pyranosides made it probable that condensation of *d*-ribose with 4 : 6-diaminopyrimidine would yield a product from which ultimately a 9-*d*-ribopyranosidoadenine (I) would be obtained rather than the natural nucleoside adenosine (II) (9-*d*-ribofuranosidoadenine). Nevertheless the possibility that such a direct synthesis might yield adenosine could not be entirely excluded on these grounds. Kuhn and Ströbele (*Ber.*, 1937, **70**, 773) observed that condensation of *o*-nitroaniline with pentoses yields *N*-pentofuranosides, and although with the diaminopyrimidines xylose yielded pyranosides we had not so far tried other pentoses. Bearing in mind the apparent tendency of ribose to form furanose derivatives as shown by their frequent occurrence in nature, it was not impossible that, unlike xylose, ribose would condense with 4 : 6-diaminopyrimidine to give a furanoside.

(I.)





(II.)

Condensation of *d*-ribose with 4 : 6-diaminopyrimidine in alcoholic solution in presence of a small amount of hydrogen chloride in the usual manner gave, in moderate yield, a crystalline 6-*amino*-4-d-*ribosidamino*-*pyrimidine*. In this case no evidence for the formation of an isomeric glycoside was obtained (cf. Part IX, preceding paper); coupling of the pure crystalline riboside or of the crystallisation residues with diazotised 2 : 5-dichloroaniline gave one and the same 6-*amino*-4-d-*ribosidamino*-5-(2′ : 5′-*dichlorobenzeneazo*)*pyrimidine*, readily acetylated to 6-*amino*-4-*triacetyl*-d-*ribosidamino*-5-(2′ : 5′-*dichlorobenzeneazo*)*pyrimidine*. Hydrogenation of the latter in presence of Raney nickel, followed by thioformylation, gave 6-*amino*-4-*triacetyl*-d-*ribosidamino*-5-*thioformamidopyrimidine*. When refluxed in dry pyridine, the thioformamido-compound evolved hydrogen sulphide, but the product did not crystallise readily; the acetyl groups were therefore removed by hydrolysis and when this had been done 9-d-*ribopyranosidoadenine* (I) was readily separated in crystalline form. The structure of the synthetic riboside follows from its hydrolysis to adenine and *d*-ribose, its insolubility in alkali, its absorption of two mols. of reagent and liberation of 1 mol. of formic acid on periodate titration, and finally from its ready deamination to 9-d-*ribopyranosidohypoxanthine*.

The results of periodate titration of the synthetic 9-*d*-ribopyranosidoadenine serve to indicate its stereochemical relationship to 9-*d*-xylopyranosidoadenine (Part IX, preceding paper). Clearly, if both glycosides have the same configuration at the glycosidic linkage, the periodate scission products should be identical, and, if not, enantiomorphous. Owing to difficulties in isolation with the small amounts employed, the scission product was not obtained in crystalline form, but the optical rotation of the periodate oxidation solution from the riboside was identical in sign and, within the rather wide limit of experimental error, in magnitude with that of the corresponding solution from the xyloside (Part IX, *loc. cit.*) at the same molar concentration. Both glycosides belong, therefore, to the same stereochemical series.

No 6-*d*-ribosidaminopurine was isolated in these synthetic experiments, although its formation was expected by analogy with the simultaneous formation of the 6- and the 9-substituted isomers in the analogous syntheses of the xylosides of adenine and 2-methyladenine (Parts VI and IX, *locc. cit.*). In view of the difficulty encountered in other cases in isolating small amounts of 6-glycosidaminopurines, however, our failure to isolate 6-*d*-ribosidaminopurine does not preclude the possibility of its formation as a by-product.

9-*d*-Ribopyranosidoadenine is very similar to adenosine in its appearance and shows virtually the same absorption spectrum. It has, however, a higher m. p., is less soluble in water, and is, as might be expected, considerably more resistant to hydrolysis by mineral acid. As the synthetic substance may differ from adenosine only in the size of the lactol ring, it may show interesting biological properties. From our results it would seem that the synthesis of adenosine and of other ribofuranosidopurines may be achieved by carrying out the initial condensation of sugar and 4 : 6-diaminopyrimidine with a 5-substituted ribofuranose rather than with *d*-ribose itself. Experiments to this end are in progress.

Experimental.

Activated alumina used throughout was prepared by heating alumina hydrate (British Aluminium Co. Ltd.) to 360° during 5 hrs.

4-*Amino*-6-d-*ribosidaminopyrimidine*.—4 : 6-Diaminopyrimidine (30 g.) and *d*-ribose (15 g.) were refluxed in absolute alcohol (1 l.) containing saturated alcoholic hydrogen chloride (10 c.c.) during 48 hrs. Dry benzene was added at intervals, and water removed azeotropically through a Fenske column with a total reflux variable take-off head. The reaction solution was filtered through activated alumina (1800 g.), and unchanged pyrimidine removed by washing the alumina with absolute alcohol (7 l.). The glycoside was eluted with water (10 l.), and the eluate concentrated in a vacuum to small bulk (100 c.c.) and kept overnight. The *riboside* separated in tiny, colourless, hydrated needles (5·6 g.), m. p. 158° (decomp.), $[\alpha]_D^{23°}$ −32° (*c*, 0·12 in water) (Found : C, 41·1; H, 5·9; N, 20·9. $C_9H_{14}O_4N_4,H_2O$ requires C, 41·5; H, 6·1; N, 21·5%).

A sample of the riboside (60 mg.) was refluxed with N/10-sulphuric acid (5 c.c.) for 30 mins., and the solution neutralised exactly with sodium hydroxide and evaporated to dryness in a vacuum. The residue was dissolved in alcohol (20 c.c.) and poured through a column of activated alumina (10 g.), and the column washed with alcohol (50 c.c.). Evaporation of the alcohol runnings gave 4 : 6-diaminopyrimidine (15 mg.), m. p. 267—268°. The column was now washed with water (50 c.c.), and the washings concentrated to small bulk (5 c.c.). Treated with phenylhydrazine in the usual way, this solution gave *d*-ribosazone (5 mg.), m. p. 163—165°, undepressed by an authentic specimen.

4-*Amino*-6-d-*ribosidamino*-5-(2′ : 5′-*dichlorobenzeneazo*)*pyrimidine*.—A solution of 2 : 5-dichloroaniline (3·3 g.) in a mixture of water (150 c.c.) and concentrated hydrochloric acid (10 c.c.) was cooled and diazotised in the usual way with sodium nitrite (1·5 g.). Finely powdered 4-amino-6-*d*-ribosidaminopyrimidine (5·5 g.) was made into a paste with a little water and added to the diazo-solution; all solid then dissolved. The solution was promptly neutralised with sodium hydrogen carbonate and after 1 hour the precipitated *azo-riboside* was collected, washed with water, and dried. Recrystallised from alcohol–pyridine, it formed yellow needles (5 g.), m. p. 225—226° (decomp.) (Found in material dried at 140° : C, 43·8; H, 4·5; N, 20·3. $C_{15}H_{16}O_4N_6Cl_2$ requires C, 43·4; H, 3·9; N, 20·2%).

4-*Amino*-6-*triacetyl*-d-*ribosidamino*-5-(2′ : 5′-*dichlorobenzeneazo*)*pyrimidine*.—(1) 4-Amino-6-*d*-ribosidamino-5-(2′ : 5′-dichlorobenzeneazo)pyrimidine (5 g.) was dissolved in dry pyridine (100 c.c.), acetic anhydride (15 c.c.) added, and the solution set aside overnight. Alcohol (20 c.c.) was added and after 1 hour the solution was evaporated in a vacuum, and the residue recrystallised from benzene. The *acetyl* derivative formed yellow needles (4·5 g.), m. p. 138° after sintering at 128° (Found in material dried at 100° : C, 46·3; H, 4·2; N, 15·8. $C_{21}H_{22}O_7N_6Cl_2$ requires C, 46·6; H, 4·1; N, 15·5%). $[\alpha]^{21°}$ −213° (*c*, 1·106 in chloroform; Wratten No. 29 filter).

(2) After removal of crystalline riboside from the reaction product of 4 : 6-diaminopyrimidine and *d*-ribose (15 g.) as above described, the aqueous mother-liquor was treated with diazotised 2 : 5-dichloroaniline in presence of sodium hydrogen carbonate. After 1 hour the crude azo-compound was collected, dried, and acetylated as described under (1) above. After destruction of the excess of acetic anhydride with alcohol and evaporation in a vacuum the residue was dissolved in ethyl acetate and chromatographed on activated alumina; development and elution were carried out with ethyl acetate. From the eluate an acetylazo-glycoside, m. p. 138°, was obtained (2·1 g.) identical with that already described; no evidence of any isomer was obtained.

4-*Amino*-6-*triacetyl*-d-*ribosidamino*-5-*thioformamidopyrimidine*.—The above acetylazo-compound (4 g.) was suspended in ethyl acetate (100 c.c.) and hydrogenated at 100°/100 atm. during 4 hrs., a Raney nickel catalyst being used. The hydrogenation solution was filtered from catalyst and evaporated in a vacuum, the residue taken up in ethyl acetate (25 c.c.) and filtered, and light petroleum (200 c.c.; b. p. 60—80°) added. The precipitated 5-amino-compound was collected, dissolved in alcohol (150 c.c.), refluxed with dithioformic acid (from 30 g. of the sodium salt) for 1 hour, a second portion of acid (from 10 g. of the sodium salt) added, heating continued for a further hour, and the mixture left overnight. Unchanged acid was filtered off and washed with hot alcohol. Filtrate and washings were evaporated in a vacuum. The residual resin crystallised on addition of alcohol and was recrystallised from alcohol. It formed colourless hydrated needles (1·6 g.) which sintered at 148° and decomposed with evolution of hydrogen sulphide at 158° (Found : C, 42·3; H, 5·0; N, 15·8. $C_{16}H_{21}O_7N_5S$, $1·5H_2O$ requires C, 42·3; H, 5·2; N, 15·4%).

9-d-*Ribopyranosidoadenine*.—The above thioformamido-compound (1 g.) was dissolved in dry pyridine (4 c.c.) and refluxed in a slow stream of nitrogen until hydrogen sulphide evolution ceased (*ca.* 14 hours). Solvent was removed in a vacuum, and the residue dissolved in a little ethyl acetate. As no crystals separated within a few hours, the ethyl acetate was removed, the residual resin dissolved in methanolic ammonia (70 c.c. saturated at 0°), and the solution kept for 60 hours. Methanol was removed on the steam-bath, and hot alcohol (20 c.c.) added to the residue. The solid which separated was recrystallised from water (yield 150 mg.). The *riboside* formed long needles which contained variable amounts of water of crystallisation. On heating it sintered somewhat at 234—235° and melted with decomp. at 254° (Found in material dried at room temp. : C, 42·7; H, 5·8; N, 25·2. $C_{10}H_{13}O_4N_5,H_2O$ requires C, 42·2; H, 5·3; N, 24·6%. Found in material dried at 140° for 4 hours : N, 26·1. $C_{10}H_{13}O_4N_5$ requires N, 26·2%). In a second experiment in which deacetylation was carried out with sodium methoxide in methanol–chloroform, 2·5 g. of the thioformamido-compound gave 350 mg. of 9-*d*-ribopyranosidoadenine; no other crystalline glycoside was isolated.

The synthetic riboside was insoluble in alkali, had $[\alpha]_D^{20°}$ −38° (*c*, 0·28 in water), and its absorption spectrum in N/10-hydrochloric acid showed a maximum at 2610 A. (ε, 19,200) and in N/10-sodium hydroxide a maximum at 2610 A. (ε, 12,600). Although unchanged on refluxing for 1 hour with N/10-sulphuric acid, the substance (50 mg.) was hydrolysed by boiling for 6 hours with N-sulphuric acid (5 c.c.). The hydrolysis solution was neutralised with dilute aqueous sodium hydroxide, and adenine picrate precipitated by adding the calculated amount of hot aqueous picric acid. It formed long yellow needles (50 mg.), m. p. 290° (decomp.). The filtrate was evaporated to dryness, and the residue extracted with boiling alcohol. The extract was evaporated, and the residue dissolved in pyridine (0·5 c.c.) and acetic anhydride (0·05 c.c.) and left at 0° overnight. On addition of a little cold water and neutralisation with sodium bicarbonate β-tetra-acetyl-*d*-ribose (*ca.* 4 mg.) separated. It had m. p. 110°, undepressed in admixture with an authentic specimen (m. p. 110°).

Periodate titration (cf. Part VIII, this vol., p. 592). Amount used, 0·0758 g. Periodate consumed, 2·01 mols./mol.; formic acid liberated, 0·99 mol./mol. Rotation of final solution +0·10° (*c*, 0·152; *l*, 2 dm.).

9-d-*Ribopyranosidohypoxanthine*.—9-*d*-Ribopyranosidoadenine (200 mg.) and sodium nitrite (400 mg.) were dissolved in water (8 c.c.) at 65°, and acetic acid (0·6 c.c.) added, gas being evolved; the temperature was maintained at 65° for 15 mins. The solution was neutralised to phenolphthalein with sodium hydroxide and evaporated to dryness in a vacuum, the residue warmed on the steam-bath for a few minutes with acetic anhydride (4 c.c.) in pyridine (10 c.c.), and the mixture left overnight. Solvent was removed in a vacuum, and the resinous residue extracted with three successive portions of boiling chloroform (30 c.c. in all). The combined extracts were evaporated on the steam-bath, and the oil so obtained deacetylated by boiling for 30 mins. with aqueous barium hydroxide (25 c.c. of a solution containing 20 g. in 300 c.c.). The calculated amount of sulphuric acid to remove barium was added, barium sulphate centrifuged off, and the

solution concentrated to small bulk in a vacuum; 9-d-*ribopyranosidohypoxanthine* then separated in colourless platelets (80 mg.), m. p. 259—260° (decomp.) (Found in material dried at 100°: C, 44·4; H, 5·0; N, 21·4. $C_{10}H_{12}O_5N_4$ requires C, 44·8; H, 4·5; N, 20·9%).

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180. *Optical Rotatory Power and Structure in Triterpenoid Compounds. Application of the Method of Molecular Rotation Differences.*

By D. H. R. BARTON and E. R. H. JONES.

Data on the optical rotatory properties of all known compounds of the triterpenoid class have been collected and analysed by what is probably best known as "the method of molecular rotation differences." This study has made possible a number of useful generalisations which, now that their existence has been revealed, will probably be confirmed and extended by future work in this field.

The molecular rotations of triterpenoid carboxylic acids and their esters are identical. The majority of the well-characterised triterpenoid compounds can be separated, according to their molecular rotation difference values, into two groups, *i.e.*, related to either the α- and β-amyrins or else to lupeol and betulin; the existence of a third, and hitherto unsuspected group, embracing a number of the less well-studied triterpenoids, is suggested. It seems highly probable that α-viscol is identical with β-amyrin, and that gratiolone and betulinic acid are one and the same substance. Very marked anomalies point distinctly to the existence of hydrogen bonding in the α- and β-boswellic acids and in echinocystic acid, and to its absence in siaresinolic acid. Hydrogenation of the easily reducible ethenoid linkage present in certain triterpenes produces characteristic molecular rotation differences and a further classification on this basis seems possible.

COMPOUNDS of the polycyclic triterpenoid (C_{30}) type are widely distributed in the vegetable kingdom, especially in resins and plant saps, where they occur in the free state, as esters, or as glycosides (saponins). Although many of them have been studied intensively during the past 15 years, in no case has the structural formula been completely elucidated. Selenium dehydrogenation, which gives mainly a variety of naphthalene compounds, has furnished useful evidence concerning the basic carbon skeletons (for summary, see Haworth, *Ann. Reports*, 1937, **34**, 327), and more recently Ruzicka and his co-workers, by means of elegant interconversions (for summary, see Spring, *ibid.*, 1941, **38**, 192; Ruzicka and Marxer, *Helv. Chim. Acta*, 1940, **23**, 144), have established simple relationships between a number of the more important members. The structural problem has thus been considerably narrowed in scope and may now be said to involve the determination of the structures of the α- and β-amyrins and of lupeol. The establishment by chemical means of the relationship of any triterpenoid compound to these three primary compounds, however, is by no means easy, since it requires a detailed knowledge of the nature and behaviour of the functional groups present. No method is as yet available for the rapid allocation of any new compound to a specific class.

Some years ago one of us observed that acetylation, benzoylation, and oxidation of various compounds derived from the triterpene alcohol, lupeol, produced regular differences in molecular rotatory power, and this suggested that a detailed survey of the literature of the triterpenes might reveal generalisations of value in connection with structural problems.

The relationship between optical rotatory power and structure in compounds of the steroid group has been examined by Wallis and his co-workers (*J. Org. Chem.*, 1941, **6**, 319; 1942, **7**, 103), who have improved upon and extended the work of Callow and Strain (*Proc. Roy. Soc.*, 1936, *A*, **157**, 194). It has been shown that, if a certain change be effected in two different steroid molecules, differing from one another in a portion of the molecule far removed from the reacting centre, then the variation in molecular rotation ($M[\alpha]$) will be approximately the same in each case. This treatment of optical rotatory phenomena in multi-acentred organic molecules is probably best termed "the method of molecular rotation differences." Its usefulness was clearly demonstrated by Wallis and his colleagues, who, by drawing up a series of constants relating each steroid to a basic stereo-skeleton, showed that the optical rotatory powers of many compounds of this group could be calculated, provided only that the relationships to a series of basic substances were known. They were able, by this means, to suggest the inaccuracy of several proposed structures. The success of this method with complex organic molecules containing many centres of asymmetry would appear to depend upon the principle of optical superposition (see, *e.g.*, Read, *Trans. Faraday Soc.*, 1930, **26**, 441), and on the "rule of shift" (Freudenberg, *Ber.*, 1933, **66**, 177; see also Levene and Meyer, *J. Amer. Chem. Soc.*, 1934, **56**, 244), according as to whether the reactions performed do or do not affect the initial molecular asymmetry. Failure to obey these two principles can usually be ascribed to "vicinal action," but Wallis and his co-workers carefully selected conditions under which this is reduced to a minimum, and in this paper also the possible operation of vicinal effects has not been overlooked, particularly where anomalies have been encountered.

Errors in the Observation of Optical Rotatory Power.—It is obviously necessary to form an estimate of the magnitude of the errors involved in routine determinations of optical rotatory power. The purity of the sample is of paramount importance, but the error due to possible impurity cannot be assessed. The actual error in measuring the rotations probably predominates over the other errors involved, *viz.*, weighing, making up of standard solutions, and variations in specific rotation with temperature and concentration. (The variation

of specific rotation with the spectral line employed and with the solvent cannot be neglected and consequently, unless otherwise specified, all values quoted are for chloroform solutions, employing the sodium D line.) A very conservative estimate of the magnitude of error to be expected in observations collected from the literature would appear to be of the order of ±4%. It is to be noted, however, that Plattner and Heusser (*Helv. Chim. Acta*, 1944, **27**, 748) have recently shown that temperature and concentration variations alone can produce an error of as much as 5%, and the above estimate of ±4% for the overall error may well be too small.

A general search of the literature has been made for the specific rotations of all triterpenoid compounds, the arithmetic means of all the recorded observations (in a few cases certain early determinations which were obviously erroneous have been neglected) have been approximated to the nearest degree, and the molecular rotations (specific rotation × molecular weight) have been rounded off to the nearest 100. (For brevity in the tables, they are divided by 100.)

I. *Triterpenoid Carboxylic Acids and their Esters.*—The molecular rotations ($M[\alpha]$) of these acids and their esters, together with the corresponding molecular rotation differences (Δ) are recorded in Table I and it is at once apparent that there is no appreciable alteration in $M[\alpha]$ on either esterification or hydrolysis. [This is

TABLE I.

Substance.	General formula of triterpenoid acid.	$10^{-2}M[\alpha]$. Acid.	Ester.		$10^{-2}\Delta$.	Refs.
Amyrin group.						
Ursolic acid	$C_{29}H_{44}(OH)(CO_2H)$: 5R, 1[=]	+319°	Methyl	+324°	+ 5°	1, 2
,, ,, acetate		+319	Ethyl	+321	+ 2	1, 3, 4, 5, 6
			n-Propyl	+319	0	
			n-Butyl	+305	− 14	
			n-Amyl	+307	− 12	
			n-Hexyl	+320	+ 1	
			n-Heptyl	+316	− 3	
			n-Octyl	+317	− 2	
β-Boswellic acid	,,	+949	Methyl	+912	− 37	7, 8, 9
		+543	,,	+522	− 21	
,, ,, acetate		+677	,,	+691	+ 14	,,
		+344	,,	+358	+ 14	
β-Amyrin group.						
α-Boswellic acid	,,	+534	,,	+541	+ 17	9
,, ,, acetate		+324	,,	+353	+ 29	,,
Glycyrrhetic acid	$C_{30}H_{44}(OH)(:O)(CO_2H)$: 5R, 1[=]	+733	,,	+765	+ 32	10, 11, 12, 13, 14, 15
			Ethyl	+757	+ 24	
,, ,, acetate		+742	Methyl	+763	+ 21	10, 11, 12, 13, 14, 15, 16
Deoxoglycyrrhetic acid acetate	$C_{32}H_{48}(OAc)(CO_2H)$: 5R, 1[=]	+578	,,	+614	+ 36	16, 17
Hederagenin	$C_{29}H_{48}(OH)_2(CO_2H)$: 5R, 1[=]	+359	,,	+355	− 4	18, 19, 20, 21
			Ethyl	+365	+ 6	
,, diacetate		+445	Methyl	+433	− 12	,, ,,
			Ethyl	+450	+ 5	
Oleanolic acid	$C_{29}H_{44}(OH)(CO_2H)$: 5R, 1[=]	+356	Methyl	+348	− 8	9, 21, 22, 23, 24, 25, 26, 27, 28, 29
,, ,, acetate		+359	,,	+348	− 11	21, 23, 24, 26, 28, 29
Siaresinolic acid	$C_{29}H_{48}(OH)_2(CO_2H)$: 5R, 1[=]		,,	+224		
			Ethyl	+225	+ 1	30, 31, 32
,, ,, 2-acetate		+252	Methyl	+253	+ 1	31
*iso*Siaresinolic acid diacetate	$C_{29}H_{46}(OAc)_2(CO_2H)$: 5R, 1[=]	+223	,,	+234	+ 12	,,
Sumaresinolic acid	$C_{29}H_{48}(OH)_2(CO_2H)$: 5R, 1[=]	+255	,,	+228	− 27	33
Echinocystic acid [1]	,,	+179	,,	+180	+ 1	34, 35
,, ,, diacetate [1]		− 83	,,	− 86	− 3	34
Lupeol–betulin group.						
Betulonic acid	$C_{29}H_{44}(:O)(CO_2H)$: 5R, 1[=]	+141	,,	+145	+ 4	36
Dihydrobetulonic acid		+ 37	,,	+ 38	+ 1	36, 37
Betulinic acid acetate	$C_{32}H_{46}(OAc)(CO_2H)$: 5R, 1[=]	+100	,,	+ 92	− 8	38, 39
Dihydrobetulinic acid acetate		− 60	,,	− 67	− 7	37
Miscellaneous group.						
*iso*Elemendionolic acid acetate	$C_{32}H_{44}(OAc)(:O)_2(CO_2H)$: 4R, 1[=]	−148	,,	−141	+ 7	40
*iso*Elemenonic acid	$C_{29}H_{47}(:O)(CO_2H)$: 4R, 1[=]	+442	,,	+447	+ 5	41
Pyroquinovic acid	$C_{29}H_{44}(OH)(CO_2H)$: 5R, 1[=]	−271	,,	−279	− 8	42
Exceptions.						
Deoxoglycyrrhetic acid	$C_{30}H_{46}(OH)(CO_2H)$: 5R, 1[=]	+675	,,	+508	−167	17
Oleanonic acid	$C_{29}H_{44}(:O)(CO_2H)$: 5R, 1[=]	+468	,,	+417	− 51	22, 23, 43
*iso*Siaresinolic acid 2-acetate	$C_{29}H_{46}(OH)(OAc)(CO_2H)$: 5R, 1[=]	+206	,,	+259	+ 53	31
Elemadienonic acid	$C_{29}H_{42}(:O)(CO_2H)$: 4R, 2[=]	+209	,,	+154	− 55	44, 45
*iso*Elemadienonic acid	,,	−304	,,	−187	+117	46, 47, 48, 49, 50
Quillaic acid [2]	$C_{29}H_{42}(OH)_2(CHO)(CO_2H)$: 5R, 1[=]	+205	,,	+272	+ 67	51, 52

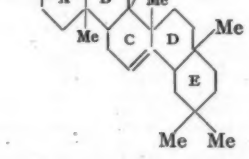
[1] In 95% EtOH; 5460 A. line. [2] In pyridine.

Refs.—(1) Huzii and Osumi, *J. Pharm. Soc. Japan*, 1939, **59**, 176. (2) Simida, *ibid.*, 1939, **59**, 619. (3) Ewen and Spring, J., 1943, 533. (4) Mendive, *J. Org. Chem.*, 1940, **5**, 235. (5) Sell and Kremers, *J. Biol. Chem.*, 1938, **125**, 451. (6) Van Haar, *Rec. Trav. chim.*, 1924, **43**, 367. (7) Simpson and Williams, J., 1938, 686, 1712. (8) Trost, *Annali Chim. Appl.*, 1937, **27**, 178. (9) Winterstein and Stein, *Z. physiol. Chem.*, 1932, **208**, 9, 56. (10) Bergman, *Biochem. Z.*, 1933, **267**, 296. (11) Karyone and Nouaka, *J. Pharm. Soc. Japan*, 1937, **57**, 166. (12) Ruzicka and Leuenberger, *Helv. Chim. Acta*, 1936, **19**, 1402. (13) Ruzicka, Furter, and Leuenberger, *ibid.*, 1937, **20**, 312. (14) Takeda, *J. Pharm. Soc. Japan*, 1938, **58**, 731. (15) Voss and Butter, *Ber.*, 1937, **70**, 1212. (16) Ruzicka and Marxer, *Helv. Chim. Acta*, 1939, **22**, 195. (17) Ruzicka, Leuenberger, and Schellenberg, *ibid.*, 1937, **20**, 1271. (18) Kitasato, *Acta Phytochim.*, 1939, **11**, 1. (19) Ruzicka and Giacomello, *Helv. Chim. Acta*, 1937, **20**, 299. (20) Van Haar and Tamburello, *Ber.*, 1921, **54**, 3148. (21) Winterstein and Stein, *Z. physiol. Chem.*, 1932, **211**, 5. (22) Jacobs and Fleck, *J. Biol. Chem.*, 1933, **98**, 341. (23) Kitasato, *Acta Phytochim.*, 1935, **8**, 207. (24) Picard, Sharples, and Spring, J., 1939, 1045. (25) Power and Tutin, J., 1908, 891. (26) Ruzicka and Giacomello, *Helv. Chim. Acta*, 1936, **19**, 1136. (27) Van Haar, *Rec. Trav. chim.*, 1928, **47**, 585. (28) Winterstein and Hämmerle, *Z. physiol. Chem.*, 1931, **199**, 60. (29) Winterstein and Stein, *ibid.*, 1931, **199**, 64. (30) Bilham, Kon, and Ross, J., 1942, 540. (31) Ruzicka, Grob, Egli, and Jeger, *Helv. Chim. Acta*, 1943, **26**, 1218. (32) Winterstein and Egli, *Z. physiol. Chem.*, 1931, **202**, 207. (33) Ruzicka, Jeger, Grob, and Hösli, *Helv. Chim. Acta*, 1943, **26**, 2283. (34) Bergsteinsson and Noller, *J. Amer. Chem. Soc.*, 1934, **56**, 1403. (35) Carson and Noller, *ibid.*, 1941, **63**, 621. (36) Ruzicka and Rey, *Helv. Chim. Acta*, 1941, **24**, 529. (37) Ruzicka, Brenner, and Rey, *ibid.*, 1941, **24**, 515. (38) Robertson, Soliman, and Owen, J., 1939, 1267. (39) Ruzicka, Lamberton, and Christie, *Helv. Chim. Acta*, 1938, **21**, 1706. (40) Ruzicka *et al.*, *ibid.*, 1943, **26**, 1659. (41) Ruzicka *et al.*, *ibid.*, 1943, **26**, 1638. (42) Wieland and Schlenk, *Annalen*, 1939, **539**, 242. (43) Kuwada and Takeda, *J. Pharm. Soc. Japan*, 1939, **59**, 131. (44) Bilham and Kon, J., 1942, 544. (45) Ruzicka and Häusermann, *Helv. Chim. Acta*, 1942, **25**, 439. (46) Lieb and Schwarzel, *Monatsh.*, 1924, **45**, 51. (47) Lieb and Mladenović, *Monatsh.*, 1932, **59**, 228. (48) Lieb and Mladenović, *ibid.*, 1933, **62**, 232. (49) Mladenović, *ibid.*, 1932, **59**, 7. (50) Ruzicka *et al.*, *Helv. Chim. Acta*, 1932, **15**, 681. (51) Elliott and Kon, J., 1939, 1130. (52) Elliott, Kon, and Soper, J., 1940, 612.

particularly well illustrated by the series of esters of ursolic acid acetate, where M varies from 526 (ethyl ester) to 610 (octyl ester) whilst $M[\alpha]$ remains constant.] On the very reasonable assumption that the specific rotations are susceptible to an error of $\pm 4\%$, the $\Delta_{M[\alpha]}$ values may deviate by some 8% from (say) the arithmetic mean of the $M[\alpha]$'s of the acid and its ester. With two exceptions, all the differences recorded in the first part of Table I are within this 8% limit, and the vast majority are even within 4%. Analysis of these 37 examples by the usual probability expression reveals that the mean error of deviation of each difference from zero is ± 250, which is insignificantly small, and that the $\Delta_{M[\alpha]}$ values are randomised homogeneously about zero.

In the second part of Table I are recorded the only cases which have been encountered where there are serious discrepancies (up to 30%) between the $M[\alpha]$'s of triterpene acids and their esters. It may well be that either the presence of impurities or inaccurate determinations are responsible, but the third alternative, that the structures of the acids and their esters are not comparable, owing possibly to double-bond migration or steric inversion on either esterification or hydrolysis, must not be overlooked. However, recent studies (Plattner and Heusser, *loc. cit.*) in the bile acid series reveal a marked $\Delta_{M[\alpha]}$ between the values for 12-hydroxy-3 : 7-diacetoxycholanic acid and its methyl ester, although special care was taken to ensure the accuracy of the specific rotations. In other similar cases in the bile acid field no appreciable $M[\alpha]$ differences were observed. A general perusal of the literature on optically active carboxylic acids leads to the conclusion that the greater the number of asymmetric centres present in the molecule, the closer becomes the correspondence between the values of $M[\alpha]_{acid}$ and $M[\alpha]_{esters}$.

II. *Triterpenoid Alcohols and their Simple Derivatives.*—As a result of the work of Ruzicka and his associates many of the triterpenoids have now been classified into one of three groups, of which the simplest members ($C_{30}H_{50}O$) are the pentacyclic monoethenoid alcohols, the α- and β-amyrins and lupeol, all three of which almost



(I.) β-Amyrin [formula suggested by Haworth (*loc. cit.*) and now favoured by the Ruzicka school].

certainly contain the secondary alcohol group in the 2-position in ring A (I). The $M[\alpha]$ differences observed with triterpene alcohols of known relative structure, when simple changes (acetylation, benzoylation, and

TABLE II.

Substance.	General formula of triterpenoid alcohol.	10^{-3} $M[\alpha]$. Alcohol.	Acetate. 1.	Benzoate. 2.	Ketone. 3.	$10^{-3}\Delta_1$.	$10^{-3}\Delta_2$.	$10^{-3}\Delta_3$.	Refs.
α-Amyrin group.[1]									
α-Amyrin	$C_{29}H_{49}(OH)$: 5R, 1|=	+358°	+370°	+498°	—	+ 12°	+140°	—	53, 54, 55, 56, 57
Ursolic acid	$C_{29}H_{49}(OH)(CO_2H)$: 5R, 1|=	+319	+319	—	—	0	—	—	1, 2, 3, 4, 6
β-Amyrin group.[1]									
β-Amyrin	$C_{29}H_{49}(OH)$: 5R, 1|=	+379	+384	+530	+454°	+ 5	+151	+ 75°	16, 54, 57, 58, 59, 60, 61, 62
Glycyrrhetic acid	$C_{29}H_{44}(OH)(CO_2H)(:O)$: 5R, 1|=	+733	+742	—	—	+ 9	—	—	10, 11, 12, 14, 16
Methyl glycyrrhetate		+765	+763	—	—	− 2	—	—	10, 11, 13, 14, 15
Oleanolic acid	$C_{29}H_{48}(OH)(CO_2H)$: 5R, 1|=	+356	+359	—	—	+ 3	—	—	9, 21, 22, 23, 24, 25, 26, 27, 28, 29
Methyl oleanolate		+348	+348	+494	+417	0	+146	+ 69	21, 22, 23, 24, 29
Methyl siaresinolate	$C_{29}H_{48}(OH)_2(CO_2Me)$: 5R, 1|=	+224	+252	—	+276	+ 28	—	+ 52	30, 31, 32, 63
Methyl sumaresinolate		+228	+217	—	—	− 11	—	—	33
Echinocystic acid [4]	$C_{29}H_{48}(OH)_2(CO_2H)$: 5R, 1|=	+179	+190	—	—	+ 11	—	—	34, 64, 65
Methyl 19-ketoechinocystate [5]	$C_{29}H_{44}(OH)(:O)(CO_2Me)$: 5R, 1|= (*a*)	− 48	—	—	+ 10	—	—	+ 58	65
	(*b*)	− 73	− 53	—	− 10	+ 20	—	+ 63	
Lupeol–betulin group.[3]									
Dihydrobetulin	$C_{30}H_{50}(OH)_2$: 5R	− 84	− 24	—	—	+ 60	—	—	37, 66, 67
Betulinaldehyde	$C_{29}H_{48}(OH)(CHO)$: 5R, 1|=	+ 84	+145	—	+232	+ 61	—	+148	36, 67, 68
Methyl betulinate	$C_{29}H_{48}(OH)(CO_2Me)$: 5R, 1|=	+ 33	+ 92	—	+145	+ 59	—	+112	36, 38, 39
Methyl dihydrobetulinate [3]	$C_{29}H_{48}(OH)(CO_2Me)$: 5R	− 90	− 67	—	+ 38	+ 23	—	+128	37
*allo*Betulin	$C_{30}H_{48}(OH)(-O-)$: 5R + Oxide R	+205	+253	+371	+356	+ 48	+166	+151	69
Lupanol	$C_{30}H_{51}(OH)$: 5R	− 77	− 9	+144	+ 68	+ 68	+221	+145	70
Lupanalol	$C_{29}H_{48}(OH)(CHO)$: 5R	+ 18	+ 68	—	—	+ 50	—	—	71
Lupeol	$C_{30}H_{49}(OH)$: 5R, 1|=	+115	+201	+318	+239	+ 86	+203	+144	54, 68, 70, 72, 73, 74, 75, 76, 77, 78
Lupenalol	$C_{29}H_{48}(OH)(CHO)$: 5R, 1|=	+ 4	+ 82	+207	—	+ 78	+203	—	79
Lupeol oxide	$C_{30}H_{49}(OH)(-O-)$: 5R + Oxide R.	+ 40	+116	—	—	+ 76	—	—	71

[1] α- and β-Boswellic acids are discussed separately in Section III. [2] The much smaller $M[\alpha]$ values in this group probably account for less accurate grouping about the mean differences. [3] The value for $M[\alpha]$ Alcohol is possibly in error (see Table VIII). [4] In 95% EtOH; 5460 A. line. [5] In dioxan : (*a*) D line, (*b*) 5460 A. line.

Refs.—(53) Bosrz and Cohen, *Arch. Pharm.*, 1912, **250**, 56. (54) Cohen, *Rec. Trav. chim.*, 1909, **28**, 370, 391. (55) Jungfleisch and Leroux, *Compt. rend.*, 1908, **147**, 862. (56) Ruzicka and Wirz, *Helv. Chim. Acta*, 1939, **22**, 948. (57) Zinke, Friedrich, and Rollett, *Monatsh.*, 1920, **41**, 253. (58) King *et al.*, *J. Amer. Chem. Soc.*, 1943, **65**, 1168. (59) Ruzicka and Schellenberg, *Helv. Chim. Acta*, 1937, **20**, 1553. (60) Ruzicka and Wirz, *ibid.*, 1940, **23**, 132. (61) Ruzicka and Wirz, *ibid.*, 1941, **24**, 248. (62) Ruzicka and Jeger, *ibid.*, 1941, **24**, 1178. (63) Ross, Ph.D. Thesis, University of London, 1943. (64) Noller and Carson, *J. Amer. Chem. Soc.*, 1941, **63**, 2238. (65) White and Noller, *ibid.*, 1939, **61**, 983. (66) Ruzicka and Isler, *Helv. Chim. Acta*, 1936, **19**, 506. (67) R. Vesterberg, *Ber.*, 1927, **60**, 1535. (68) Ruzicka and Brenner, *Helv. Chim. Acta*, 1939, **22**, 1523. (69) Schulze and Pieroh, *Ber.*, 1922, **55**, 2332. (70) Heilbron, Kennedy, and Spring, J., 1938, 329. (71) Ruzicka and Rosenkranz, *Helv. Chim. Acta*, 1939, **22**, 778. (72) Cohen, *Arch. Pharm.*, 1907, **245**, 238. (73) Dieterle, *ibid.*, 1923, **261**, 89. (74) Jungfleisch and Leroux, *Compt. rend.*, 1907, **144**, 1435. (75) Likiernik, *Ber.*, 1891, **24**, 183. (76) Sugii, Sengoku, and Taguchi, *J. Pharm. Soc. Japan*, 1931, **51**, 847. (77) Swift and Walter, *J. Amer. Chem. Soc.*, 1942, **64**, 2539. (78) Van Romburgh, *Ber.*, 1894, **27**, 3441. (79) Jones and Meakins, J., 1940, 1335.

oxidation) are effected at this 2-position, are given in Table II, and on using these criteria, two main groupings are clearly discernible:

	Δ_{acetyl}.	$\Delta_{benzoyl}$.	Δ_{ketone}.
α- and β-Amyrin group	+ 600°	+14,500°	+ 6000°
Lupeol–betulin group	+7000	+20,000	+14,000

The almost complete identity of the $\Delta_{M[\alpha]}$ values in the α- and β-amyrin series suggests that, identical carbon skeletons being assumed (which is by no means certain), the ethenoid linkages in both series are sufficiently far removed from ring A so that " vicinal action " with the 2-hydroxyl group cannot occur. In the steroid field, Bernstein, Wilson, and Wallis (*J. Org. Chem.*, 1942, **7**, 103) observed a negligible influence of ethenoid linkages in the 8 : 14- and the 14 : 15-position on the C_3 centre, whereas 7 : 8- and 8 : 9-bonds appeared to exert an appreciable effect. On this basis it might be suggested that in neither α- nor β-amyrin can the double bond be located in ring A or B, a suggestion which is in accord with the bulk of the chemical evidence.

Table III gives the data for triterpenoids whose inter-relationships have yet to be established, grouped

TABLE III.

Substance.	General formula of triterpenoid alcohol.	$10^{-3}M[\alpha]$. Alcohol.	Acetate.	Benzoate.	Ketone.	$10^{-3}\Delta_1$.	$10^{-3}\Delta_2$.	$10^{-3}\Delta_3$.	Refs.
			1.	2.	3.				
Amyrin type.									
α-Viscol	$C_{30}H_{49}(OH)$: 5R, 1|=	+362°	+374°	—	—	+ 12°	—	—	80
Lanosterol	$C_{30}H_{49}(OH)$: 4R, 2|=	+247	+262	+392°	+307°	+ 15	+145°	+ 60°	81, 82, 83
Lupeol–betulin type.									
Gratiolone methyl ester	$C_{30}H_{48}(OH)(CO_2Me)$: 5R, 1|=	+ 24	+100 [1]	—	—	+ 76	—	—	84
Polyporenic acid A methyl ester	$C_{30}H_{45}(OH)_2(CO_2Me)$: 4R, 2|=	+374	+465	—	—	+ 91	—	—	85
Possible new type.									
Euphol	$C_{30}H_{49}(OH)$: 4R, 2|=	+136	+192	—	—	+ 56	—	—	86
Germanicol	$C_{30}H_{49}(OH)$: (?) 5R, 1|=	+ 26	+ 84	+207	—	+ 58	+181	—	87
Scandol	$C_{30}H_{49}(OH)$: (?) 5R, 1|=	+243	+286	+392	—	+ 43	+149	—	88
Skimmiol	$C_{30}H_{49}(OH)$: 5R, 1|=	+ 13	+ 66	+191	—	+ 53	+178	—	89
Taraxasterol	,,	+409	+473	+567	+466	+ 64	+158	+ 57	90, 91, 92
ψ-Taraxasterol	,,	+200	+248	+371	—	+ 48	+171	—	90, 93
Cryptosterol	$C_{30}H_{49}(OH)$: 4R, 2|=	+251	+300	+376	+322	+ 49	+125	+ 71	94
Miscellaneous.									
Agnosterol	$C_{30}H_{49}(OH)$: 4R, 3|=	+301	+424	+549	—	+123	+248	—	82, 83
Basseol	$C_{30}H_{49}(OH)$: 4R, 2|=	− 51	+ 94	—	—	+145	—	—	95, 96
Elemadienolic acid	$C_{30}H_{45}(OH)(CO_2H)$: 4R, 2|=	−105	−209	—	+209	−104	—	+314	44, 45, 97
*epi*Elemadienolic acid	,,	+ 46	+130	—	+209	+ 84	—	+163	44, 45
Elemenolic acid	$C_{30}H_{49}(OH)(CO_2H)$: 4R, 1|=	− 73	−160	—	+169	− 87	—	+242	44, 45, 47, 98, 99
Euphorbol	$C_{30}H_{49}(OH)$: 4R, 2|=	0	0	—	—	0	—	—	86
Taraxol	$C_{30}H_{47}(OH)O_2$: 5R, 1|=	+359	+466	—	—	+107	—	—	90
β-Viscol	$C_{30}H_{49}(OH)$: 5R, 1|=	+239	+201	—	—	− 38	—	—	80

[1] Value for gratiolone acetate.

Refs.—(80) Bauer and Gerloff, *Arch. Pharm.*, 1936, **274**, 473. (81) Dorée and Garrett, *J. Soc. Chem. Ind.*, 1933, **52**, 141, 355. (82) Ruzicka, Rey, and Muhr, *Helv. Chim. Acta*, 1944, **27**, 472. (83) Windaus and Tschesche, *Z. physiol. Chem.*, 1930, **190**, 51. (84) Maurer, Meier, and Reiff, *Ber.*, 1939, **72**, 1870. (85) Cross, Eliot, Heilbron, and Jones, J., 1940, 632. (86) Newbold and Spring, J., 1944, 249. (87) Simpson, J., 1944, 283. (88) Cook *et al.*, *J. Amer. Pharm. Assoc.*, 1944, **33**, 15. (89) Takeda, *J. Pharm. Soc. Japan*, 1941, **61**, 63. (90) Burrows and Simpson, J., 1938, 2042. (91) Power and Browning, J., 1912, 2411. (92) *Idem*, J., 1914, 1829. (93) Morice and Simpson, J., 1940, 795. (94) Wieland *et al.*, *Annalen*, 1937, **529**, 68. (95) Beynon, Heilbron, and Spring, J., 1937, 989. (96) Heilbron, Moffett, and Spring, J., 1934, 1583. (97) Lieb and Mladenović, *Monatsh.*, 1932, **61**, 274. (98) Lieb and Mladenović, *ibid.*, 1931, **58**, 59. (99) Ruzicka *et al.*, *Helv. Chim. Acta*, 1932, **15**, 1454.

TABLE IV.

Substance.	α-Viscol. M. p.	α-Viscol. [α]D.	β-Amyrin. M. p.	β-Amyrin. [α]D.	Ref.	Substance.	α-Viscol. M. p.	α-Viscol. [α]D.	β-Amyrin. M. p.	β-Amyrin. [α]D.	Ref.
Alcohol	200°	+85°	201—203°	+89°	16	Ketone	181°	—	178—180°	—	100
			198—199		59				177—179		101
			199—200		58				177—178		102
Acetate	241	+80	241—242	+82	16				186		60
			240—241		59	Ketone oxime	256	—	262—263	—	100
			242		60				265—267		101
			241—242		62	Ketone semi-carbazone	245	—	244—245	—	103
			238—239		58				244—245		102
			238—240						248—249		60
Benzoate	240	—	233—234	—	16	Diene (from alcohol with PCl_5)	169	+120° [1]	175—178	+112° [1]	104
			235—236		60				173—175		105
			223—224		58				170—175		106
			232—233								

[1] In C_6H_6; other rotations in $CHCl_3$.

Refs.—(100) A. Vesterberg, *Ber.*, 1891, **24**, 3837. (101) Rollett, *Monatsh.*, 1923, **43**, 413. (102) Ruzicka, Schellenberg, and Goldberg, *Helv. Chim. Acta*, 1937, **20**, 791. (103) Horrmann and Firzlaff, *Arch. Pharm.*, 1930, **268**, 64. (104) A. Vesterberg, *Ber.*, 1887, **20**, 1245. (105) Ruzicka, Silbermann, and Furter, *Helv. Chim. Acta*, 1932, **15**, 483. (106) Winterstein and Stein, *Annalen*, 1933, **502**, 223.

TABLE V.

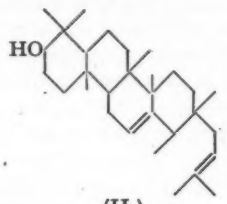
	Gratiolone (Ref. 84). M. p. [1]	Gratiolone (Ref. 84). [α]D.	Betulinic acid. (Ref. 39). M. p. [2]	Betulinic acid. (Ref. 39). [α]D.	Betulinic acid. (Ref. 38). M. p. [4]	Betulinic acid. (Ref. 38). [α]D.	Betulinic acid. (Ref. 107). M. p. [5]
Acid	311—312°	+ 6° [6]	295—297°	—	316—318°	+ 8° [6]	315—317°
Acetate	268 [1]	+20	288—290	+20°	289—291	+ 8	290—292
Methyl ester	220	+ 5	224—225	+ 5	223—224	+ 8	223—225
Methyl ester acetate	197	—	200—202	+17	201—202	+18	202—203
Acetate bromolactone	186	+13	—	—	290 (d.)	—	293—296 (d.)

[1] The low m. p. is almost certainly due to contamination with the mixed anhydride, known to be readily formed from betulinic acid unless special precautions are taken. [2] Presumably uncorrected. [3] Corrected. [4] Uncorrected. [5] Probably uncorrected. [6] In pyridine.

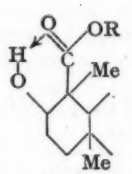
Ref.—(107) Kawaguti and Kim, *J. Pharm. Soc. Japan*, 1940, **60**, 343.

according to the magnitude of their $M[\alpha]$ differences. α-Viscol falls into the amyrin group, and a careful comparison (Table IV) with β-amyrin indicates that the two substances must almost certainly be identical. Rather surprisingly, the possibility of this identity does not appear to have been considered by the original investigators (Bauer and Gerloff, *Arch. Pharm.*, **1936**, **274**, 473), although the reactions of α-viscol and β-amyrin are more or less identical. Again, gratiolone, which falls into the lupeol–betulin group, is almost certainly identical with betulinic acid (Table V)—the one or two reported discrepancies between the two substances would probably be eliminated on more deliberate investigation.

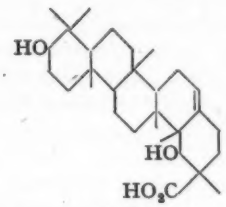
It is difficult to believe that the close agreement between the $M[\alpha]$ differences of lanosterol and those of the amyrins is entirely fortuitous. It seems reasonable to suppose that if ring E of the pentacyclic (say) β-amyrin system were opened (as in II), this change would have comparatively little effect on the $M[\alpha]$ differences produced by reactions at the remote 2-position, and formulations such as (II), which explain many of the reactions of lanosterol, might be considered.



(II.)



(III.)



(IV.)

The $M[\alpha]$ difference data also suggest a relationship between polyporenic acid A (Cross, Eliot, Heilbron, and Jones, J., 1940, 632; Cross and Jones, *ibid.*, p. 1491) and the lupeol–betulin group. This is by no means unlikely, for the acid is obtained from a fungus parasitic on the birch tree, the bark of which contains a high proportion of betulin.

As is indicated in Table III, some 6 triterpenoids have $M[\alpha]$ differences of the same order, but yet entirely distinct from those of the amyrin and the lupeol group (Δ_{acetyl} 5500°; $\Delta_{benzoyl}$ 16,000°; Δ_{ketone} 6500°), and, although future investigations may require a revision of some of the values, it seems reasonable to suggest that we have here an entirely new group of triterpenoids.

III. *Hydrogen Bonding in Triterpenoid Carboxylic Acids.*—Ruzicka has converted the α- and β-boswellic acids into the β- and α-amyrins respectively, but the $M[\alpha]$ difference data recorded in Table VI reveal, instead of the expected small increases, large *decreases* in $M[\alpha]$ on acetylation, benzoylation, and oxidation of the boswellic acids and their esters. These anomalies can almost certainly be attributed to the existence of hydrogen bonding, as indicated in (III), in the acids and esters, and the inhibition of this bonding on esterification or oxidation of the 2-hydroxyl group. It is to be noted that normal $M[\alpha]$ differences are observed with the decarboxylated β-boswellic acid derivatives (nor-β-boswellenol, etc.) in which hydrogen bonding is, of course, impossible. Echinocystic acid (IV, according to Kon) is also known to contain a hydroxyl group in the β-position to the carboxyl group, and White and Noller (*J. Amer. Chem. Soc.*, **1939**, **61**, 983) have already tentatively suggested the existence of hydrogen bonding. This is clearly indicated by the large decreases in $M[\alpha]$ both on acetylation and on oxidation of the second hydroxyl group (Table VI). Similar effects will

TABLE VI.

Substance.	General formula of triterpenoid alcohol.	$10^{-3}M[\alpha]$. Alcohol.	Acetate. 1.	Ketone. 2.	$10^{-3}\Delta_1$.	$10^{-3}\Delta_2$.	Refs.
α-Amyrin group.							
β-Boswellic acid	$C_{29}H_{44}(OH)(CO_2H)$: 5R, 1[=]	+949°	+677°	+577°	−272°	−372°	7, 8, 9
		+543	+344	—	−199	—	
Methyl β-boswellate		+912	+691	—	−221	—	7, 9
		+522	+358	—	−164	—	
Nor-β-boswellenol	$C_{29}H_{47}(OH)$: 5R, 1[=]	+461	+495	+525	+ 34	+ 64	7, 8[1]
β-Amyrin group.							
α-Boswellic acid	$C_{29}H_{44}(OH)(CO_2H)$: 5R, 1[=]	+524	+324	—	−200	—	9
Methyl α-boswellate		+541	+353	—	−188	—	9
Echinocystic acid acetate[1]	$C_{29}H_{43}(OH)(OAc)(CO_2H)$: 5R, 1[=]	+190	− 83	—	−273	—	34, 64, 65
,, methyl ester[2]		(*a*) +148	—	− 53	—	−201	,,
		(*b*) +174	− 86	− 95	−260	−269	

[1] In 95% EtOH; 5460 A. line. [2] In dioxan: (*a*) D line, (*b*) 5460 A. line.

TABLE VII.

Substance.	General formula of triterpenoid alcohol.	$10^{-3}M[\alpha]$. Alcohol.	Diacetate. 1.	Diketone. 2.	$10^{-3}\Delta_1$.	$10^{-3}\Delta_2$.	Refs.
Methyl echinocystate[1]	$C_{29}H_{43}(OH)_2(CO_2Me)$: 5R, 1[=]	+180°[2]	—	− 73°[2]	—	−253°	34, 35, 64, 65
Methyl siaresinolate	,,	+224	—	+665	—	+441	30, 31, 32
Echinocystic acid 2-acetate[1]	$C_{29}H_{43}(OH)(OAc)(CO_2H)$: 5R, 1[=]	+190[2]	− 83°[2]	—	−273°	—	34, 64, 65
*iso*Siaresinolic acid 2-acetate	,,	+206	+222	—	+ 16	—	31
Methyl echinocystate 2-acetate[1]	$C_{29}H_{43}(OH)(OAc)(CO_2Me)$: 5R, 1[=]	+148[3]	—	(ketoacetate) − 53[3]	—	−201	34, 64, 65
Methyl *iso*siaresinolate 2-acetate	,,	+259	—	(ketoacetate) +326	—	+ 67	31

[1] 5460 A. line. [2] In 95% EtOH. [3] In dioxan.

undoubtedly be observed with quillaic acid (which is closely related to echinocystic acid) when sufficient data are available.

Two alternative formulations for siaresinolic acid have been put forward, by Ruzicka and Kon respectively, and in that due to the latter, hydrogen bonding between the second hydroxyl group and the carboxyl group would certainly be expected. The comparison given in Table VII of the $M[\alpha]$ differences in the siaresinolic and echinocystic acid series does not indicate any hydrogen bonding in the former case, and suggests that in respect of the relative positions of the second hydroxyl and carboxyl groups, the Ruzicka formulation is preferable, although the possible interference by steric factors cannot be overlooked entirely.

It should be noted, in connection with this postulation of the existence of hydrogen bonding in the triterpene series, that Rule and his collaborators (J., 1929, 401, 2516) made a similar suggestion to explain abnormal optical rotatory phenomena observed with the *l*-menthyl esters of salicylic and 1-hydroxy-2-naphthoic acids and their methyl ethers.

IV. *Triterpenoids with Easily Reducible Ethenoid Linkages.*—Triterpenes of the lupeol–betulin group and also the majority of the tetracyclic triterpenes possess, in striking contrast to those of the amyrin type, a readily reducible double bond. The $M[\alpha]$ differences consequent upon hydrogenation of this ethenoid linkage are quoted in Table VIII, from which it is immediately apparent that the $\Delta_{M[\alpha]}$ value of about −19,000° for lupeol

TABLE VIII.

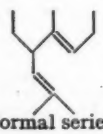
Substance.	General formula of triterpenoid.	$10^{-3}M[\alpha]$. Triterpene.	Dihydro.	$10^{-3}\Delta$.	Refs.
Basseol acetate	$C_{30}H_{49}(OAc)$: 4R, 2|=	+ 94°	+155°	+ 61°	95, 96
Betulin	$C_{30}H_{49}(OH)_2$: 5R, 1|=	+ 66	− 84	−150	66, 67
,, diacetate		+116	− 37	−153	66, 67, 69
Methyl betulinate [1]	$C_{29}H_{49}[OH](CO_2Me)$: 5R, 1|=	+ 24	− 90	−114	37, 39
,, ,, acetate		+ 87	− 67	−154	,,
Betulonic acid	$C_{29}H_{45}(:O)(CO_2H)$: 5R, 1|=	+141	+ 37	−104	36
Methyl betulonate		+145	+ 38	−107	36, 37
Lupadiene	$C_{30}H_{48}$: 5R, 2|=	+102	− 81	−183	70
Lupeol	$C_{30}H_{49}(OH)$: 5R, 1|=	+115	− 77	−192	68, 70, 72, 74, 75, 76, 77, 78
,, acetate		+201	− 9	−210	68, 70, 73, 76, 77
,, benzoate		+318	+144	−174	54, 68, 70, 76
Lupeone	$C_{30}H_{48}(:O)$: 5R, 1|=	+259	+ 68	−191	68, 70, 76
α-Lupene [2]	$C_{30}H_{50}$: 5R, 1|=	+115	− 4	−119	70, 108
Lupenalol	$C_{30}H_{48}(OH)(CHO)$: 5R, 1|=	+ 4	+ 18	+ 14	71, 79
,, acetate		+ 82	+ 68	− 14	,,
Lupenediol [2]	$C_{30}H_{48}(OH)_2$: 5R, 1|=	− 18	+ 22	+ 40	109

[1] It has been suggested (Table III) that the $M[\alpha]$ value for methyl dihydrobetulinate is erroneous. A correction to −12,000° results in uniformity both here and in the previous table.
[2] In view of the good agreement between other values in this series it seems probable that one of the rotation values is incorrect. [3] In pyridine.
Refs.—(108) Ruzicka and Rosenkranz, *Helv. Chim. Acta*, 1940, **23**, 1311. (109) Meakins, Ph.D. Thesis, University of London, 1941.

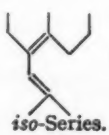
and most of its derivatives is highly characteristic. Exceptions are observed only in those compounds where the methyl group in the α-position to the olefinic linkage in the *iso*propenyl side chain (–CMe:CH_2) is substituted, as in lupenalol, –C(CHO):CH_2, and in lupenediol, –C(CH_2OH):CH_2. This profound discrepancy may find interpretation either in (*a*) the asymmetric synthesis consequent upon the introduction of a new asymmetric centre upon reduction of the olefinic linkage or in (*b*) the operation of a " vicinal effect."

The $\Delta_{M[\alpha]}$ values for betulin and its derivatives range around −15,000°, and the difference from the lupeol value may also be attributed to a " vicinal effect " between the primary carbinol group and the olefinic linkage, the possibility of which is clearly apparent in the partial formulation (V) for betulin (Ruzicka and Rey, *Helv. Chim. Acta*, 1943, **26**, 2143).

(V.)



Normal series.



iso-Series.

(VI.)

According to the data in Table IX for triterpenoids of unknown and as yet unrelated structure, there is a distinct similarity between agnosterol, lanosterol, and cryptosterol. The first two have been correlated (Markes, Wittle, and Mixon, *J. Amer. Chem. Soc.*, 1937, **59**, 1368) and the last two are already known to posses

TABLE IX.

Substance.	General formula of triterpenoid.	$10^{-3}M[\alpha]$. Triterpene.	Dihydro.	$10^{-3}\Delta$.	Refs.
Agnosterol	$C_{30}H_{47}(OH)$: 4R, 3|=	+301°	+260°	− 41°	82, 83
,, acetate		+424	+393	− 31	82, 83
Cryptosterol	$C_{29}H_{45}(OH)$: 4R, 2|=	+251	+231	− 20	94
,, acetate		+300	+249	− 51	,,
,, benzoate		+376	+383	+ 7	,,
Lanosterol	,,	+247	+223	− 24	81, 82, 83
,, acetate		+262	+249	− 13	81, 83
Polyporenic acid A methyl ester	$C_{30}H_{45}(OH)_2(CO_2Me)$: 4R, 2|=	+374	+371	− 3	85
Elemadienolic acid	$C_{29}H_{43}(OH)(CO_2H)$: 4R, 2|=	−105	− 73	+ 32	44, 47, 97, 98, 99
*epi*Elemadienolic acid	,,	+ 46	+ 64	+ 18	45
Elemadienonic acid	$C_{29}H_{43}(:O)(CO_2H)$: 4R, 2|=	+209	+169	− 40	44, 45
*iso*Elemadienonic acid	,,	−304	−427	−123	41, 46, 49, 50, 97

many similarities, and both yield acetone as an ozonolysis product; possibly agnosterol will likewise be found to contain an *iso*propylidene grouping.

The marked distinction between the $\Delta_{M[\alpha]}$ values in the elemadienolic acid series is doubtless related to the position of the second, non-reducible double bond (see VI), and may well be due to the operation of a " vicinal effect."

V. *Triterpenoid Diols and their Simple Derivatives.*—Although a detailed examination of the literature on these compounds has been made, sufficient data are not yet available on the mono- and di-esters and similar derivatives for any relationships which might exist to become apparent.

Conclusions.—In view of the multiplicity and possible magnitude of the sources of error inherent in routine specific rotation determinations, and also of the many experimental difficulties encountered in obtaining triterpenoid compounds in an analytically pure condition, the regularities now brought to light are remarkable. Just as in the steroid field, $M[\alpha]$ differences appear to be characteristic of the basic stereo-skeleton of the molecule, and by careful determinations of the molecular rotations of the simple derivatives obtained in the preliminary stages of routine structural investigations, determinations which result in only a negligible consumption of material, much information concerning the fundamental structural unit involved may be forthcoming. The possible identities of α-viscol and gratiolone with β-amyrin and betulinic acid, respectively, only became apparent after these compounds had been classified according to their $M[\alpha]$ differences, and these cases provide good examples of the general usefulness of this new method of attack. The constancy of molecular rotations on esterification and hydrolysis of triterpene acid derivatives, the relatively facile diagnosis of hydrogen bonding in hydroxy-acids, and the characteristic $M[\alpha]$ differences observed on hydrogenation of lupeol and elemadienolic acid derivatives, all represent useful additions to the present state of knowledge of triterpene chemistry. It seems certain that future observations in this field will confirm, extend, and more completely systematise the regularities already brought to light in the present investigation, and that further rules relating structure to optical rotatory properties will undoubtedly emerge.

The authors thank Professor I. M. Heilbron, D.S.O., F.R.S., for his unfailing interest and encouragement, and Professor G. A. R. Kon, F.R.S., and Dr. W. C. J. Ross for valuable discussions.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY, LONDON, S.W.7. [*Received, September 28th*, 1944.]

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181. *Delphinium Alkaloids. Part III. Delpheline.*

By JOHN A. GOODSON.

Delpheline has the formula $C_{25}H_{39}O_6N$ and not $C_{22}H_{33}O_5N$ previously assigned to it.

DELPHELINE, a base isolated from the alkaloids of *Delphinium elatum*, L., and assigned the formula $C_{22}H_{33}O_5N$ (Goodson, J., 1943, 139), has been found by potentiometric titration to have a molecular weight of 450, agreeing well with that required for the formula $C_{25}H_{39}O_6N$ and confirmed by the analytical figures found for the hydrochloride and nitrate previously recorded (Goodson, *loc. cit.*, p. 141) and by the fact that six oxygen atoms can now be accounted for. Of these, three were known to be present in methoxyl groups, two are now found in a methylenedioxy-group, and one is shown to occur in a hydroxyl group, by the preparation of a monoacetyl derivative. The substance, like aconine (Jacobs and Elderfield, *J. Amer. Chem. Soc.*, 1936, 58, 1059), contains an ethylimino-, not a methylimino-group as formerly assumed.

EXPERIMENTAL.

Detection of the Methylenedioxy-group.—Delpheline gives Gaebel's test for this group (Found by the method of Clowes and Tollens, *Ber.*, 1899, **32**, 2847: CH_2O_2, 9·7. Calc. for $C_{25}H_{39}O_6N$: CH_2O_2, 10·2%).

Detection of the Ethylimino-group.—Delpheline was heated with hydriodic acid in a Herzig and Meyer apparatus and when all the methyl iodide arising from the action of the acid on the methoxyl groups had been removed the residue in the distillation flask was heated with hydriodic acid and ammonium iodide, and the evolved alkyl iodide collected in ice-cold dry alcohol. The solution was heated with excess of trimethylamine for 4 hours at 50°. Evaporation of the solvent left trimethylethylammonium iodide [Found: I, 58·8. Calc. for NMe_2EtI: I, 59·0%. Found for delpheline: NEt, 9·65; equiv., by potentiometric titration with N/10-hydrochloric acid, 450. Calc. for $C_{25}H_{39}O_6N$: NEt, 9·58%; equiv., 449].

The following analytical figures previously recorded (Goodson, *loc. cit.*, p. 141) are given for comparison with those calculated for salts of a base having formula $C_{25}H_{39}O_6N$: Delpheline hydrochloride (Found: C, 59·5; H, 8·3; N, 3·1; Cl, 7·1; OMe, 18·6; NEt, 8·4. Calc. for $C_{25}H_{39}O_6N,HCl,H_2O$: C, 59·5; H, 8·4; N, 2·8; Cl, 7·0; 3OMe, 18·5; NEt, 8·5%). Delpheline nitrate (Found: C, 58·7; H, 7·8; N, 5·7; OMe, 19·8; NEt, 7·4. Calc. for $C_{25}H_{39}O_6N,HNO_3$: C, 58·5; H, 7·9; N, 5·5; 3OMe, 18·2; NEt, 8·4%).

Acetyldelpheline.—Delpheline (0·5 g.) was heated with acetyl chloride (4 c.c.) for 1 hour at 50°. The excess of acetyl chloride was removed, and the residue treated with water (20 c.c.) and excess of sodium bicarbonate. The *acetyl* compound, extracted with ether and recrystallised from dilute alcohol, gave anhydrous prisms (0·42 g.), m. p. 125° (sintering at 123°), $[\alpha]_D^{20°}$ −34·5° (c = 2 in dry alcohol) (Found: Ac, 8·75. $C_{25}H_{39}O_6NAc$ requires Ac, 8·8%).

Delpheline in acetic acid solution was not hydrogenated when shaken with palladium-black in the presence of hydrogen.

The author thanks Mr. F. J. Peters for assistance with the work.

THE WELLCOME LABORATORIES OF TROPICAL MEDICINE, LONDON, N.W. 1. [*Received, September 27th*, 1944.]

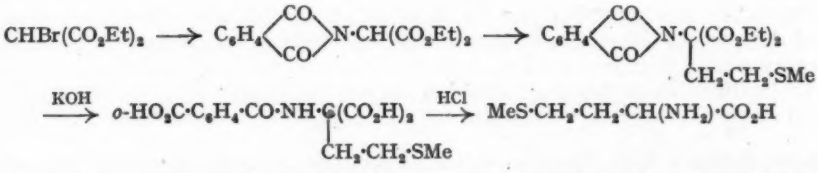
182. *The Synthesis of α-Amino-acids. Part I.* dl-*Methionine.*

By E. Booth, V. C. E. Burnop, and W. E. Jones.

The preparation of *dl*-methionine has been investigated on the large laboratory scale, a modification of the published method starting from ethyl bromomalonate being used. The overall yield is approximately 40%.

Beattie and Marshall (*Nature*, 1944, **153**, 525) have indicated the value of methionine in the treatment of certain types of jaundice, and the synthesis of this compound on a comparatively large scale has been investigated. The following routes are described in the literature: (*a*) From β-chloropropaldehyde diethylacetal (Barger and Coyne, *Biochem. J.*, 1928, **22**, 1417); overall yield, 3%. (*b*) From methyl β-chloroethyl sulphide by a malonic ester synthesis (Windus and Marvel, *J. Amer. Chem. Soc.*, 1930, **52**, 2575); yield, 8%. (*c*) Condensation of methyl β-chloroethyl sulphide with ethyl phthalimidomalonate, hydrolysis, and decarboxylation (*Organic Syntheses*, Coll. Vol. II, 384); yield, 50%, calculated on methyl β-chloroethyl sulphide. (*d*) From α-benzamido-γ-butyrolactone *via* ethyl α-benzamido-γ-methylthiobutyrate (Hill and Robson, *Biochem. J.*, 1936, **30**, 248); yield, 3%. (*e*) From 3 : 6-bis-β-chloroethyl-2 : 5-diketopiperazine (Snyder and Cannon, *J. Amer. Chem. Soc.*, 1944, **66**, 511); yield, 60%.

Owing to either inaccessibility of starting materials or poor yields, methods (*a*), (*b*), (*d*) and (*e*) were considered unsuitable for large-scale operation and attention was concentrated on method (*c*), which involves the following stages:



The following are the most important modifications made in the method described in the literature: (1) Methyl β-hydroxyethyl sulphide is more conveniently obtained from monothioethylene glycol and methyl sulphate than from sodium methyl mercaptide and ethylene chlorohydrin.* (2) It is essential that methyl β-chloroethyl sulphide should not be distilled at pressures above 30 mm., otherwise decomposition occurs, giving rise to impurities in the methionine, which are difficult to remove (cf. Snyder, Howe, Cannon, and Nyman, *J. Amer. Chem. Soc.*, 1944, **66**, 511). (3) An 80% yield of ethyl phthalimidomalonate is obtained by heating together phthalimide, ethyl bromomalonate, and sodium carbonate in xylene. Agitation must be very efficient and the sodium carbonate must be finely divided. The condensation of ethyl bromomalonate with potassium phthalimide (isolated) cannot be carried out with safety on a large scale. (4) Isolation of ethyl sodium phthalimidomalonate is unnecessary. It can be formed in alcoholic solution with sodium ethoxide, and the condensation with methyl β-chloroethyl sulphide carried out in the same solution.

The following derivatives of *dl*-methionine have been prepared: (a) *ethyl* ester, b. p. 112°/2·5 mm.; (b) N-*cinnamoyl*, m. p. 162—164°; (c) 2 : 5-*dibromobenzenesulphonate*, m. p. 186°; (d) 3 : 4-*dichlorobenzenesulphonate*, m. p. 183°.

Experimental.

Ethyl Phthalimidomalonate.—A suspension of anhydrous sodium carbonate (1590 g.) and phthalimide (2940 g.; 20 mols.) in dry xylene (7 l.) was refluxed with vigorous stirring in a 20-litre three-necked flask, and ethyl bromomalonate (4780 g.; 20 mols.) added during ½—1 hr. After being heated and stirred for a further 4 hrs., the mixture was cooled to 35°, filtered, and the cake washed with xylene (1 l.). The combined washings and filtrate were evaporated to about two-thirds and treated with stirring at 30° with light petroleum (5 l., b. p. 40—60°). After cooling below 20°, the phthalimidomalonic ester was obtained as a pale brown, crystalline powder on filtration and washing with light petroleum. During recovery of the mixed solvents a further quantity of the product was obtained, raising the yield to approx. 80%.

Methyl β-Chloroethyl Sulphide.—A solution of monothioethylene glycol (780 g.; 10 mols.) in aqueous sodium hydroxide (450 g. in 3 l. of water) was treated gradually with methyl sulphate (945 c.c.) below 30° with stirring. After standing overnight, the solution was extracted with chloroform (4 × 1 l.), and solvent distilled from the extracts until the volume had been reduced to about 2 l. To the stirred solution, thionyl chloride (1200 g.), diluted with its own volume of chloroform, was added at such a rate as to keep the mixture refluxing gently. Stirring and refluxing were continued for a further 2 hrs., and the solution then cooled, washed successively with water, dilute sodium hydroxide solution, and water, and dried over calcium chloride. Removal of the solvent and distillation of the residue at 30 mm. gave the product as an oil, b. p. 58°. The yield varied from 70—90% depending on the quality of the monothioethylene glycol.

3-Methylthio-1-phthalamidopropane-1 : 1-dicarboxylic Acid.—A solution of sodium (144 g.) in absolute alcohol (2·25 l.) was added during a few minutes with stirring to a warm solution of ethyl phthalimidomalonate (1900 g.; 6·2 mols.) in absolute alcohol (2 l.) in a 20-litre flask. The solution was then refluxed with stirring while methyl β-chloroethyl sulphide (690 g.; 6·2 mols.) was added during 1½ hrs. The mixture was refluxed for a further 3 hrs. and cooled, and water (13 l.) added, stirring being continued for a further ½ hr. The oily layer was then separated, dissolved in alcohol (2·25 l.), and refluxed with stirring for 3 hrs. after addition of 30% aqueous potassium hydroxide (6·25 l.). After cooling, ice (7 kg.) was added, and the solution made acid to Congo-red with concentrated hydrochloric acid (2·6—3 l.), the temperature not being allowed to exceed 3°. The solution was run into a mixture of concentrated hydrochloric acid (2·5 l.) and water (10 l.) and maintained below 5° overnight; the product was then collected and air-dried. The yield was 75—80%, the product containing less than 2% of potassium chloride.

dl-*Methionine.*—The tricarboxylic acid (1·6 kg.) was added to a mixture of concentrated hydrochloric acid (4 l.) and water (4 l.) in a 20-litre flask and carefully heated with stirring. Decarboxylation proceeded smoothly and was completed by boiling for 2 hrs. On cooling, phthalic acid separated; it was removed and washed with a little cold water. The

* The authors are indebted to Mr. L. J. Lermit for this information.

combined aqueous liquor was evaporated to dryness under reduced pressure, and the residue dissolved in hot water (0·6 l.), poured into a mixture of pyridine (1·25 l.) and alcohol (6·25 l.), and allowed to crystallise. The crude material was recrystallised (charcoal) from water (6 l.), giving pure *dl*-methionine (390 g.); a further quantity (approx. 85 g.) remained in the mother-liquor and was obtained on concentration, the total yield therefore being 64%. The product crystallised in small plates and was free from potassium chloride and " bimethionine " (Snyder, Howe, Cannon, and Nyman, *loc. cit.*) (Found: S, 21·3; N, 9·3. Calc. for $C_5H_{11}O_2NS$: S, 21·5; N, 9·4%). It formed an N-*cinnamoyl* derivative crystallising from aqueous alcohol in plates, m. p. 162—164° (Found: S, 11·2; N, 4·8. $C_{14}H_{17}O_3N$ requires S, 11·5; N, 5·0%).

dl-*Methionine Ethyl Ester*.—A suspension of methionine (25 g.) in absolute alcohol (150 c.c.) was saturated at 0° with hydrogen chloride and then refluxed for 1 hr. The solvent was removed in a vacuum, and the residue treated with saturated aqueous potassium carbonate and extracted with ether. The ethereal solution was dried over anhydrous sodium sulphate, the solvent removed, and the residue distilled, giving an 88% yield of the *ethyl* ester as a viscous oil, b. p. 112°/2·5 mm., $d_4^{20°}$ 1·0670, $n_D^{20°}$ 1·4819 (Found: N, 7·9. $C_7H_{15}O_2NS$ requires N, 7·9%).

dl-*Methionine* 2 : 5-*Dibromobenzenesulphonate*.—Methionine (3 g.) was added to a solution of 2 : 5-dibromobenzenesulphonic acid (7 g.) in water (20 c.c.), and the mixture warmed until a clear solution was obtained. After standing overnight at 0°, *methionine* 2 : 5-*dibromobenzenesulphonate* separated in fine needles, which were collected and washed twice with ice-water. Yield, 83%. M. p. 186°, not raised by recrystallisation from water (Found: N, 3·0; S, 14·2; Br, 34·7. $C_{11}H_{15}O_5NS_2Br_2$ requires N, 3·0; S, 13·8; Br, 34·4%). The corresponding 3 : 4-*dichlorobenzenesulphonate*, prepared in 80% yield in the same way, was obtained as a micro-crystalline powder, m. p. 183° (Found: N, 3·7; S, 17·1; Cl, 18·7. $C_{11}H_{15}O_5NS_2Cl_2$ requires N, 3·7; S, 17·0; Cl, 18·9%).

The authors wish to thank Messrs. R. E. Dewhirst, J. F. Jackson, A. Nightingale, and C. Powney for assistance and the Director General of Scientific Research and Development, Ministry of Supply, for permission to publish this work.

RESEARCH ESTABLISHMENT, SUTTON OAK. [*Received, August 31st*, 1944.]

183. *The Conversion of Sucrose into Furan Compounds. Part I. 5-Hydroxymethylfurfuraldehyde and Some Derivatives.*

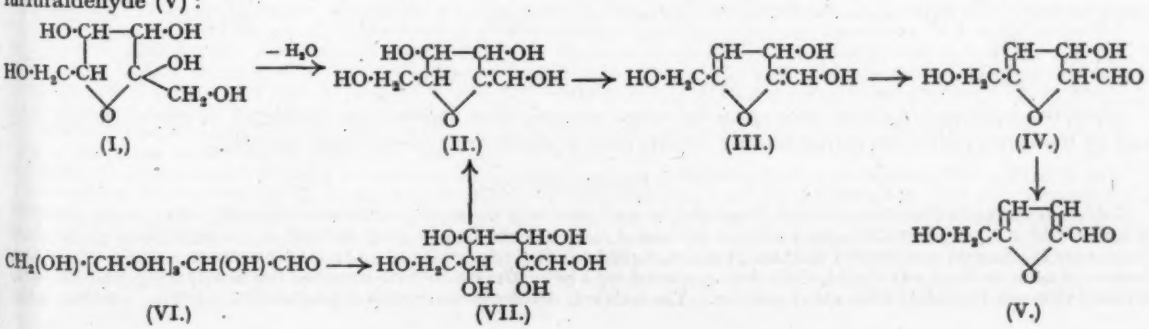
By W. N. HAWORTH and W. G. M. JONES.

Treatment of sucrose in aqueous solution with 0·25% oxalic acid leads to the formation of 5-hydroxymethylfurfuraldehyde and it has been shown that only the fructose half of the sucrose molecule takes part in this reaction. The conversion of glucose into 5-hydroxymethylfurfuraldehyde has been brought about by the pretreatment of its aqueous solution with alkali and the subsequent treatment with 0·25% oxalic acid. Improvements in the preparation of 5-chloromethylfurfuraldehyde from sucrose and several new 2 : 5-disubstituted derivatives of furan are described.

THE preparation and properties of 5-hydroxymethylfurfuraldehyde have been investigated with a view to its providing a source of useful organic intermediate compounds. The conversion of sucrose into 5-hydroxymethylfurfuraldehyde has been described previously (Düll, *Chem. Ztg.*, 1895, **216**; Kiermayer, *ibid.*, p. 1003; Middendorp, *Rec. Trav. chim.*, 1919, **38**, 1) and the method used in this investigation was based on the procedure of Kiermayer.

Sucrose was treated with oxalic acid in aqueous solution under pressure under various conditions; the results are in Table II. The maximum yield obtained amounted to 54% of the theoretical (calculated on the amount of fructose present). The product was a brown, mobile oil which could be purified by distillation in a good vacuum, with a small amount of decomposition only, provided that the distillation was carried out in an oxygen-free atmosphere immediately upon isolation of the crude product. The special apparatus described by Middendorp (*loc. cit.*) for the distillation of 5-hydroxymethylfurfuraldehyde was found to offer no advantages. That only the fructose portion of the sucrose molecule reacts with oxalic acid solution under these conditions was demonstrated by the oxidation with nitric acid of the residual solution after the removal of the 5-hydroxymethylfurfuraldehyde. Potassium hydrogen saccharate was obtained in practically the same yield as that obtained in previous experiments from pure glucose (Haworth and Jones, this vol., p. 65). It therefore appears that the reaction between oxalic acid and sucrose under these conditions is such that the fructose half of the sucrose molecule only is utilised, leaving the glucose portion unattacked.

This is explained by the fact that the fructose part of the sucrose molecule is initially in the furanose form and under the acid conditions continues to exist in this form in equilibrium with the pyranose form. Thus by the following scheme (I ⟶ V) fructose (I) in the furanose form can be converted into 5-hydroxymethylfurfuraldehyde (V):



Moreover it was envisaged that this reaction could take place with glucose (VI) if the latter could be made to react in its enolic form (VII), which by loss of water would give (II) intermediate in the conversion of fructose into hydroxymethylfurfuraldehyde. This being the case, preliminary treatment of glucose with alkali, followed by acid treatment, would provide the required conditions for its conversion into 5-hydroxymethylfurfuraldehyde.

The formation of the enolic form (VII) as a first stage of the treatment of glucose with alkali was first postulated by Lobry de Bruyn and van Eckenstein (*Rec. Trav. chim.*, 1895, **14**, 195) and later by Nef (*Annalen*, 1907, **357**, 295) and the action of alkali on glucose has more recently been studied by Evans (*J. Amer. Chem. Soc.*, 1926, **48**, 2665) and by Wolfrom and Lewis (*ibid.*, 1928, **50**, 842).

Evans and co-workers have investigated the action of potassium hydroxide on aqueous solutions of glucose and have utilised the formic acid ultimately produced as an index of the amount of 1 : 2 ene-diol present in the reaction products. Treatment of aqueous solutions of glucose with potassium hydroxide under various conditions, and subsequent treatment of the neutralised solutions of the reaction products with 0·25% oxalic acid as in the case of sucrose, led to the isolation of 5-hydroxymethylfurfuraldehyde as anticipated. Thus the amount of hydroxymethylfurfuraldehyde isolated from the reaction products after treatment with acid also provided an index of the amount of 1 : 2 ene-diol produced by the initial reaction with alkali. To obtain the maximum yields of hydroxymethylfurfuraldehyde, the treatment of glucose with alkali must be directed towards ensuring the maximum amount of 1 : 2 ene-diol formation. Table I shows the amounts of hydroxymethylfurfuraldehyde isolated from the products of reaction of glucose (100 g.) with potassium hydroxide in water (300 c.c.), followed by treatment with oxalic acid as above described.

TABLE I.

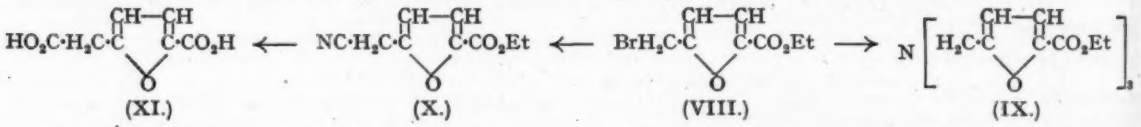
Wt. of KOH, g.	5·0	5·0	2·0	1·0
Time, hrs.	48	24	16	24
Temp. of alkali treatment	50°	50°	50°	50°
Final yield of 5-hydroxymethylfurfuraldehyde, g.	12	10	10	5

Similarly glucose was pretreated with calcium hydroxide solution at 35° for 10 days and after neutralisation with oxalic acid the products were treated with 0·25% oxalic acid as in the case of sucrose itself, and 5-hydroxymethylfurfuraldehyde isolated. The aqueous solution, after the extraction of the latter compound, was again treated with calcium hydroxide, and a further quantity of hydroxymethylfurfuraldehyde obtained. As a result of four such treatments hydroxymethylfurfuraldehyde was obtained from glucose to the extent of 28·5% of the theoretical yield.

The conversion of glucose into 5-hydroxymethylfurfuraldehyde might also be brought about in one stage by the action of suitable buffers. Treatment of glucose with disodium hydrogen phosphate under various conditions gave in one instance 5-hydroxymethylfurfuraldehyde in small yield, but these experiments sufficed to show that no appreciable conversion of glucose into 5-hydroxymethylfurfuraldehyde could be effected in this manner.

Fenton *et al.* (J., 1901, **79**, 808; 1909, **95**, 1334) have described the preparation of 5-chloromethylfurfuraldehyde from keto-hexoses, sucrose, and cellulose by the action of hydrogen chloride in an inert solvent. Optimum conditions for the reaction have been obtained by saturating a suspension in carbon tetrachloride of a concentrated aqueous solution of sucrose with hydrogen chloride. 5-Chloromethylfurfuraldehyde was isolated from the product in 21·3% yield, based on the whole sucrose molecule. It was converted into 5-hydroxymethylfurfuraldehyde in 90% yield by hydrolysis with boiling water by the method of Cooper and Nuttall (J., 1912, **101**, 1075). However, the overall yield of 5-hydroxymethylfurfuraldehyde from sucrose in this way does not compare with that obtained by the direct treatment of sucrose with oxalic acid.

5-Hydroxymethylfurfuraldehyde was oxidised to 5-hydroxymethylfuran-2-carboxylic acid by the method of Reichstein (*Helv. Chim. Acta*, 1926, **9**, 1066) and from it the hitherto undescribed *ethyl* ester has been prepared. The *5-chloromethyl* and corresponding *bromo*-derivatives of the ester were readily prepared from the hydroxy-derivative by the use of the appropriate halogen acid in dry ether. The halogen is extremely reactive and treatment of *ethyl 5-bromomethylfuran-2-carboxylate* (VIII) with concentrated aqueous ammonia in the cold gave almost immediately the crystalline tertiary amine, *tri-(2-carbethoxy-5-furfuryl)amine* (IX).



(XI.) (X.) (VIII.) (IX.)

Ethyl 5-cyanomethylfuran-2-carboxylate (X) was prepared from the bromo-derivative in the usual manner, and on hydrolysis gave the corresponding dibasic acid, *furan-2-carboxylic-5-acetic acid* (XI).

EXPERIMENTAL.

5-Hydroxymethylfurfuraldehyde.—(a) *From the fructose portion of the sucrose molecule.* Sucrose (100 g.) was dissolved in water (300 c.c.), hydrated oxalic acid (0·7 g.) added, and the solution heated to 145° in an autoclave, maintained thereat for 15 minutes and then at 125° for 2½ hours, cooled to room temperature, and neutralised with calcium carbonate. Basic lead acetate (5 g.) was added, the solution stirred for 1 hour, the precipitate removed by centrifuging, and the clear filtrate extracted (Soxhlet) with ethyl acetate. The extract, dried over anhydrous magnesium sulphate, yielded, after

distillation of the solvent, a brown syrup which crystallised slowly at 0°. Yield, 20 g. The material distilled at 110°/0·02 mm. as a light yellow, mobile liquid, crystallising immediately at 0°, m. p. 31·5°, $n_D^{18°}$ 1·5627. It was soluble in alcohol, acetone, ether, and chloroform, very slightly soluble in light petroleum (b. p. 60—80°), and gave a semicarbazone, m. p. 192° (Found : C, 45·9; H, 5·0; N, 23·1. Calc. for $C_7H_9O_2N_3$: C, 45·9; H, 4·9; N, 23·0%). The function of the basic lead acetate in the isolation of 5-hydroxymethylfurfuraldehyde was to remove an impurity, extractable from the aqueous solution with ethyl acetate, the presence of which completely inhibited crystallisation of the aldehyde. The effect of variations in the conditions of preparation of 5-hydroxymethylfurfuraldehyde is shown in Table II.

TABLE II.

Treatment of Sucrose with Oxalic Acid in Aqueous Solution under Various Conditions.

The experiments were performed on 100 g. of sucrose in each case and the yield represents the amount of crystalline product obtained after distillation of the ethyl acetate extraction solvent.

Vol. of solution, c.c.	Wt. of oxalic acid, g.	Time, hrs.	Temp.	Pressure, atms.	Atmosphere.	5-Hydroxymethylfurfuraldehyde, g.
200	0·6	2·5	135—140°	4·5	Air	12·2
300	,,	,,	130—135	,,	,,	13·0
200	0·7	,,	135—140	,,	,,	12·3
250	,,	2·0	135—140	,,	,,	13·0
,,	,,	2·5	125—130	3·5	,,	11·0
,,	,,	,,	155° for 15 mins., then maintained at 120—125°	3·0	,,	0·0
300	,,	,,	130—135	4·0	,,	13·3
,,	,,	2·0	130—135	,,	,,	15·0
,,	,,	2·5	125—130	3·5	,,	16·0
,,	,,	,,	145° for 15 mins., then maintained at 125°	3·0	,,	20·0
,,	,,	,,	160° for 15 mins., then maintained at 135—140°	4·5	,,	15·0
200	0·8	,,	135—140	,,	,,	11·7
300	,,	,,	115—120	1·5	,,	0·0
,,	,,	,,	135—140	5·5	Nitrogen	14·0
,,	,,	,,	135° for 15 mins., then maintained at 120—125°	3·0	Air	13·0
,,	,,	2·0	130—140	4·5	,,	15·0
,,	,,	2·5	130—135	,,	Nitrogen	12·5
,,	,,	,,	100—105	28·0	,,	1·25
,,	1·26	,,	135—140	4·5	Air	9·0
,,	,,	,,	145—150	6·0	,,	9·0
,,	,,	1·5	155—160	7·5	Nitrogen	8·5
,,	1·4	2·5	145—150	7·0	,,	10·0
,,	,,	,,	135—140	5·5	,,	9·5

(b) *From the glucose portion of the molecule.* (i) *By preliminary treatment of glucose with calcium hydroxide.* Glucose (200 g.) was dissolved in an aqueous solution of calcium hydroxide (600 c.c., saturated at 35°), and xylene (1 c.c.) added. The solution was heated at 35° for 10 days, and aqueous oxalic acid then added until the pH was equal to that of a 0·25% solution of oxalic acid. Calcium oxalate was removed on the centrifuge, and the clear brown solution heated in an autoclave at 130—135° for 3 hours. The solution, after cooling, was neutralised with calcium carbonate and extracted (Soxhlet) with ethyl acetate. 5-Hydroxymethylfurfuraldehyde (18·5 g.) was isolated as previously described.

The residues from the above preparation were concentrated on the boiling water-bath to 300 c.c., and all traces of ethyl acetate removed. Calcium hydroxide was added in amount sufficient to give a saturated solution at 35°, and the solution heated for 10 days at this temperature. 5-Hydroxymethylfurfuraldehyde was isolated as described above. As the result of four such treatments the yield of the aldehyde from 200 g. of glucose was 40 g. (28·5% of the theoretical).

(ii) *By preliminary treatment of glucose with potassium hydroxide.* Quantities of glucose (100 g.) were dissolved in water (300 c.c.), and potassium hydroxide, in amounts indicated by Table I, added. The resultant solutions were heated at 50° for various times as shown, and thereafter in each case brought to pH 7 by addition of dilute hydrochloric acid. An aqueous solution of oxalic acid was then added until the pH was equivalent to that of a 0·25% solution of oxalic acid. The solutions were then heated at 135—140° for 3 hours in an autoclave and subsequently treated for the isolation of 5-hydroxymethylfurfuraldehyde as previously described.

Treatment of Glucose with Disodium Hydrogen Phosphate.—Glucose (25 g.) was dissolved in water (75 c.c.), and disodium hydrogen phosphate (9 g.) added. The solution was heated in a sealed tube at 185° for 3 hours. Black humous material was deposited and the solution was acidic at the end of the reaction. It was treated for the isolation of 5-hydroxymethylfurfuraldehyde as above described. Yield, 0·7 g.

Isolation of Potassium Hydrogen Saccharate from the Glucose Portion of the Sucrose Molecule after Conversion of the Fructose Portion into 5-Hydroxymethylfurfuraldehyde.—The aqueous solution, after the extraction of 5-hydroxymethylfurfuraldehyde (*vide supra*), was concentrated to 250 c.c. Nitric acid (160 c.c., *d* 1·42) was added, and the solution heated on the boiling water-bath; vigorous oxidation took place. The nitric acid was then boiled off as completely as possible with repeated additions of water. The syrupy residue finally obtained was diluted and kept for 12 hours. The solution was filtered, neutralised at 70° with potassium hydroxide solution, rendered faintly alkaline, and cooled to 0°. On addition of glacial acetic acid in moderate excess, potassium hydrogen saccharate crystallised. Yield, 30 g. (43·5% of the theoretical), equiv., 252 (calc., 248), $[\alpha]_D^{20°}$ + 5·1° (*c*, 1·0).

Glucose (50 g.) on oxidation under precisely similar conditions gave potassium hydrogen saccharate in a yield of 31 g.

Conversion of Sucrose into 5-Chloromethylfurfuraldehyde.—The conditions used for the optimum yield of product were as follows : Cane sugar (30 g.) was dissolved in water (20 c.c.), and carbon tetrachloride (250 c.c.) added. Hydrogen chloride was passed through the mechanically stirred mixture for 1 hour, the temperature then raised to 40°, and stirring continued for 4 hours. The volume of carbon tetrachloride solution was maintained at 250 c.c. by frequent additions. After standing for 12 hours, the carbon tetrachloride solution was decanted, and the dark syrupy residue re-treated as above described. The carbon tetrachloride solutions were combined, neutralised with sodium bicarbonate, and dried

over anhydrous magnesium sulphate. Distillation of the carbon tetrachloride left a dark mobile syrup. It distilled in a vacuum and was obtained as a colourless liquid, crystallising completely at 0°. Yield, 5·4 g. (21·3% of the theoretical), m. p. 37°.

Conversion of 5-Chloromethylfurfuraldehyde into 5-Hydroxymethylfurfuraldehyde.—The method described by Cooper and Nuttall (*vide supra*) was used. The 5-chloromethyl-aldehyde was added to a large excess of boiling water, and the 5-hydroxymethyl-aldehyde extracted with ethyl acetate. Yield, 90% of the theoretical.

Ethyl 5-Hydroxymethylfuran-2-carboxylate.—5-Hydroxymethylfuran-2-carboxylic acid, prepared from 5-hydroxymethylfurfuraldehyde (Reichstein, *loc. cit.*), was refluxed for 7 hours in 1% ethyl-alcoholic hydrogen chloride. The resultant solution was neutralised with lead carbonate, and the residue obtained after distillation of the ethyl alcohol fractionally distilled under reduced pressure. The *ester*, b. p. 120—130° (bath temp.)/0·02 mm., was obtained as a mobile liquid which crystallised completely on standing. Recrystallised from ether–light petroleum, it had m. p. 46° (Found: C, 56·5; H, 5·95; OEt, 27·1. $C_8H_{10}O_4$ requires C, 56·5; H, 5·9; OEt, 26·5%).

5-Hydroxymethylfuran-2-carboxyamide.—This was prepared from the ethyl ester by treatment with ethyl-alcoholic ammonia. The solid product, recrystallised from methyl alcohol–ether, had m. p. 151—152°.

Ethyl 5-Chloromethylfuran-2-carboxylate.—Ethyl 5-hydroxymethylfuran-2-carboxylate (1 g.) was dissolved in carbon tetrachloride (40 c.c.) and refluxed while dry hydrogen chloride was passed in until the solution was saturated. The solution was kept at 0° for 12 hours, neutralised with sodium bicarbonate, and dried over anhydrous magnesium sulphate. Distillation of the carbon tetrachloride left a mobile syrup which partly crystallised. It was triturated with ether–light petroleum, and the insoluble unchanged starting material (0·6 g.) removed by filtration. Distillation of the ether and light petroleum left a mobile liquid (0·4 g.), which was ethyl 5-chloromethylfuran-2-carboxylate, $n_D^{20°}$ 1·5103, b. p. (bath temp.) 115°/0·015 mm.

Ethyl 5-Bromomethylfuran-2-carboxylate.—Ethyl 5-hydroxymethylfuran-2-carboxylate was added to a 50% solution of hydrogen bromide in dry ether and kept at 0° for 2 days. The solution was then neutralised with sodium bicarbonate and dried over anhydrous magnesium sulphate. Distillation of the ether gave ethyl 5-bromomethylfuran-2-carboxylate in 90% of the theoretical yield. It was a mobile, yellow liquid, b. p. (bath temp.) 125°/0·005 mm., $n_D^{18°}$ 1·5414.

Ethyl 5-Cyanomethylfuran-2-carboxylate.—Ethyl 5-bromomethylfuran-2-carboxylate (2 g.) was dissolved in alcohol (2 c.c.) and added gradually to a solution of sodium cyanide (0·5 g.) in water (1 c.c.). The mixture was refluxed on a boiling water-bath for 2 hours and then filtered. Water was added, and the mixture extracted with ether. Distillation of the ether gave a mobile liquid, b. p. 120° (bath temp.)/0·012 mm. The colourless liquid crystallised on standing at 0°, and was recrystallised from ether–light petroleum; yield, 1·4 g., m. p. 42—43°.

Furan-2-carboxylic-5-acetic Acid.—The preceding ester (0·5 g.) was dissolved in ethyl alcohol (1·5 c.c.) and added to sodium hydroxide (0·4 g.) dissolved in water (0·5 c.c.). The whole was boiled under reflux for 24 hours, insoluble material separating after 2 hours' boiling. Alcohol was removed by evaporation, the residue dissolved in the minimum amount of water, and the free acid precipitated by addition of 60% sulphuric acid. The crystalline material was removed by filtration and recrystallised from hot water, forming fine needles, m. p. 217°. Yield, almost quantitative (Found: C, 50·0; H, 3·7. $C_7H_6O_5$ requires C, 49·5; H, 3·5%).

Tri-(2-carbethoxy-5-furfuryl)amine.—Ethyl 5-bromomethylfuran-2-carboxylate (0·5 g.) was added to concentrated aqueous ammonia (20 c.c.) and kept at 40° for 2 days. The solid product was removed by filtration and recrystallised from ether–light petroleum. The product (0·2 g.) was obtained in long, white needles, m. p. 76° [Found: C, 60·9; H, 5·8; N, 3·6; OEt, 28·2. $(C_9H_9O_3)_3N$ requires C, 60·9; H, 5·7; N, 3·0; OEt, 28·5%].

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A. E. Hills Laboratories,
The University, Edgbaston, Birmingham.

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184. *The Condensation Products of the 1 : 2-Disubstituted 3-Nitrosoindoles A New Type of Cyanine Dye.*

By Frederick G. Mann and R. Colin Haworth.

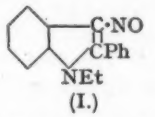
It is shown that 2-aryl-1-alkyl- and 1 : 2-diaryl-indoles react with nitrous acid to give green crystalline 3-nitroso-derivatives. 1-Alkyl-2-methyl- and 1-aryl-2-methyl-indoles give, however, green dinitroso-derivatives, the nitrous acid attacking the 2-methyl group as well as the 3-position in the indole ring. The 3-nitrosoindoles condense readily with the quaternary salts of many suitable heterocyclic compounds having reactive methyl groups: *e.g.*, 3-nitroso-2-phenyl-1-ethylindole (I) condenses with α-picoline methiodide, furnishing (*2-phenyl-1-ethyl-3-indole*)(*1-methyl-2-pyridine*)-*α-azadimethincyanine iodide* (IV). Many compounds of this type have been prepared; they represent a novel type of cyanine dye, and possess photo-desensitising properties. Variation of the quaternary salts employed and of the substituents in both reactants will thus provide a wide range of these cyanine dyes for photographic application.

The 3-nitrosoindoles also condense with other compounds containing a reactive methylene group, *e.g.*, ethyl cyanoacetate, dibenzoylmethane, to give simple anil-like condensation products. The nitrosoindoles oxidise other methylene compounds; *e.g.*, they convert thioindoxyls into the corresponding thioindigotins: the initial reaction here is doubtlessly also condensation to form an anil, which then reacts with unchanged thioindoxyl to give the thioindigotin and the aminoindole.

It has been shown by Campbell and Cooper (J., 1935, 1208) and by Womack, Campbell, and Dodds (J., 1938, 1402) that nitrous acid converts 2-phenyl-1-methylindole into the green crystalline 3-nitroso-2-phenyl-1-methylindole, the properties of which were studied. Crowther, Mann, and Purdie (J., 1943, 58) showed that the formation of these green 3-nitroso-derivatives was a general reaction of 2-aryl-1-alkylindoles; many such derivatives were prepared as a ready method of characterising the parent indoles. They also obtained a green nitroso-derivative from 2-phenyl-5-methyl-1-ethylindole, and we have now obtained a similar derivative from *5-ethoxy-2-phenyl-1-ethylindole*: these results, by excluding the 5-position for the nitroso-group, confirm the allocation of this group to the 3-position by Campbell and his co-workers.

We have now investigated in detail, first, the extent to which the formation of these green 3-nitrosoindoles is dependent on the nature of the substituents in the 1- and 2-positions, and secondly, certain condensation reactions which the 3-nitroso-group in these compounds undergoes.

On the first point, three other classes of indoles had to be studied, namely, 1 : 2-diaryl-, 1 : 2-dialkyl-, and 1-aryl-2-alkyl-indoles. We have found that 1 : 2-*diphenylindole* readily gave the green 3-*nitroso*-1 : 2-*diphenylindole*, which has many of the chemical properties of, *e.g.*, 3-nitroso-2-phenyl-1-ethylindole (I) : it is clear, therefore, that 1 : 2-diarylindoles behave similarly to the original 2-aryl-1-alkylindoles. The examples we have taken of the remaining two classes of indoles were 1 : 2-dimethylindole and 1-*phenyl*-2-*methylindole* : these both behaved abnormally, however, for the only product in each case that we have been able to isolate by the action of nitrous acid was a crystalline green *dinitroso*-derivative. Since direct nitrosation of the benzene ring in substituted indoles has not been observed under these conditions, it is almost certain that these two products, formulated in their (probably more stable) tautomeric form, are 3-*nitroso*-1-*methyl*-2-*oximinomethylindole* (II) and 3-*nitroso*-1-*phenyl*-2-*oximinomethylindole* (III) respectively. It is probable that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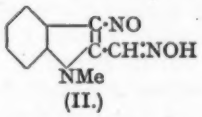
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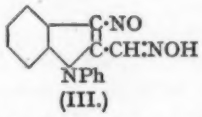
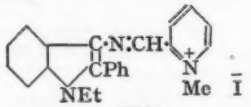

(III.)

this abnormal formation of these dinitroso-derivatives is peculiar to those 1 : 2-dialkyl- and 1-aryl-2-alkyl-indoles which have a 2-methyl group, since the latter is probably more reactive towards nitrous acid than any other alkyl group. We intend later to prepare indoles of these two types having alkyl groups other than methyl in the 2-position, in order to determine this point.

For investigating the condensation reactions of these 3-nitroso-derivatives, we have selected 3-nitroso-2-phenyl-1-ethylindole (I) for our main study. We have confirmed Campbell's observation that these nitroso-derivatives do not apparently condense with primary amines. When, however, this nitroso-compound was treated with α-picoline methiodide in alcoholic solution containing a trace of piperidine, ready condensation occurred, with the formation of the intensely coloured (2-*phenyl*-1-*ethyl*-3-*indole*)(1-*methyl*-2-*pyridine*)-α-*azadimethincyanine iodide* (IV). This compound represents an entirely novel type of cyanine dye : it has the conjugate linkage characteristic of this class of compound, and the cation also clearly exists as a resonance hybrid of the two forms (IV) and (IV*A*). Quinaldine methiodide similarly gave (2-*phenyl*-1-*ethyl*-3-*indole*)(1-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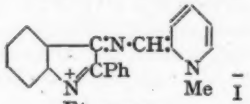
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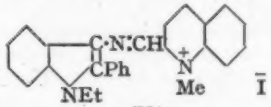
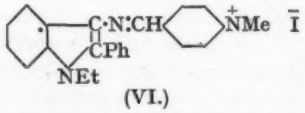

(V.)

methyl-2-*quinoline*)-α-*azadimethincyanine iodide* (V). Many similar compounds have been prepared, in view of the importance of these compounds in photographic chemistry. γ-Picoline methiodide also condensed with the nitrosoindole under the influence of piperidine to give the corresponding (1-*methyl*-4-*pyridine*) *iodide* (VI)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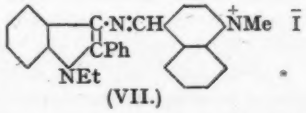
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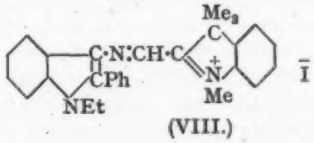
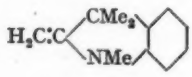

(VIII.)

and lepidine methiodide gave the (1-*methyl*-4-*quinoline*) *iodide* (VII). In view of these results, it might have been expected that either or both of the methyl groups in 2 : 4-dimethylpyridine methiodide would condense with the nitroso-indole : no condensation product could be isolated, however.

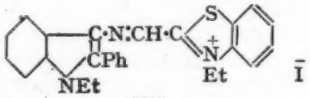
There is little doubt that in the above reactions the piperidine exercises its normal function in such condensations; *e.g.*, that it reacts with the α-picoline methiodide to give piperidine hydriodide and 1-methyl-2-methylenepyridine; the latter then condenses with the nitrosoindole, and the product at once reclaims hydrogen iodide from the piperidine salt to give the stable cyanine (IV). It is noteworthy that 2 : 3 : 3-trimethylindolenine methiodide readily condensed, without a catalyst, to give (2-*phenyl*-1-*ethyl*-3-*indole*)(1 : 3 : 3-*trimethyl*-2-*indolenine*)-α-*azadimethincyanine iodide* (VIII). This ready condensation was not unexpected, because the indolenine methodide is known to lose hydrogen iodide easily, giving 1 : 3 : 3-trimethyl-2-methyleneindoline (IX) : consequently a boiling alcoholic solution of the methiodide undoubtedly contains traces of hydrogen iodide and the reactive indoline (IX) and conditions for condensation, with subsequent recombination with the hydrogen iodide, must be ideal. The pure indoline (IX) in alcoholic solution would not condense with the nitroso-indole. This was also not unexpected, because the condensation product, had it been formed, would have been devoid of the stabilising effect of the resonance—and in effect of all the characteristic structural features—of cyanine compounds : its formation therefore would proceed only if an acid (*e.g.*, hydrogen iodide) were present for immediate union to give the stable cyanine (as VIII).

The reactivity of heterocyclic oxygen and sulphur compounds having apparently suitable methyl groups

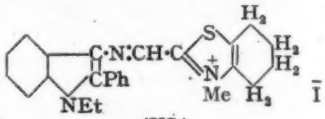
for condensation with the nitrosoindole is noteworthy. The methiodides of 2-methyloxazoline and of 2-methylbenzoxazole gave no condensation, in spite of a wide variety of conditions utilised. On the other hand, the ethiodide of 2-methylbenzthiazole and the methiodide of 2-methyltetrahydrobenzthiazole readily condensed, giving the (1-*ethyl*-2-*benzthiazole*) *iodide* (X) and the (1-*methyl*-2-*tetrahydrobenzthiazole*) *iodide* (XI) respectively: furthermore, 2-methylbenzselenazole methiodide similarly furnished the (1-*methyl*-2-*benzselenazole*) *iodide* (as X). In contradistinction to these results, however, no condensation could be



(IX.)

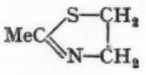


(X.)

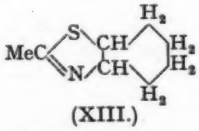


(XI.)

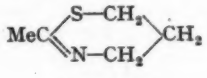
effected with the quaternary salts of 2-methylthiazoline (XII), 2-methylhexahydrobenzthiazole (XIII) or 2-methyldihydro-1 : 3-thiazine (XIV). It would appear, therefore, that the 2-methyl group in this type of heterocyclic compound will react with the nitrosoindole only if the nitrogen and sulphur atoms are linked through two carbon atoms, and if the latter in turn are joined by a double bond. This lack of reactivity in the quaternary salts of (XIV) is, however, in marked contrast to the results of Hamer and Rathbone (J.,



(XII.)



(XIII.)



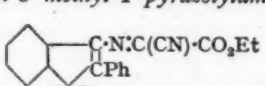
(XIV.)

1943, 243), who showed that the methiodide of (XIV) condensed with ethyl orthoformate in pyridine solution to give bis-2-(3-methyldihydro-1 : 3-thiazine)trimethincyanine iodide.

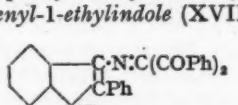
Many condensation products similar to those formulated above have been prepared from 3-nitroso-2-*p*-chlorophenyl-1-ethylindole, from 3-nitroso-1 : 2-diphenylindole, and from the 1-methyl-dinitroso-derivative (II), but only ill-defined derivatives have been obtained from the 1-phenyl-dinitroso-derivative (III).

It is known that, when in cyanine dyes the chain of atoms linking the two heterocyclic nuclei is composed solely of :CH· groups, *i.e.*, is a pure methin chain, the dyes almost always possess photo-sensitising properties, but when this chain contains nitrogen atoms as well as :CH· groups, the dyes may have either photo-sensitising or photo-desensitising properties on the normal photographic plate. Kendall (*J. Soc. Dyers and Col.*, 1936, **52**, 13) has suggested as an empirical rule that, when the nitrogen atom in the chain is separated from the nitrogen atoms of the heterocyclic nuclei by an odd number of carbon atoms, the compound will be a photo-sensitiser: when, however, this nitrogen atom is separated from either of the " heterocyclic " nitrogen atoms by an even number of carbon atoms, the compound will be a photo-desensitiser. In all the members of our new type of cyanine dyes (IV—XI) the nitrogen atom of the chain is separated from *both* heterocyclic nitrogen atoms by an even number of carbon atoms, and on Kendall's rule the compounds should be desensitisers. The action of these compounds on the photographic plate has been investigated by the staff of Imperial Chemical Industries Ltd. (Dyestuffs Division), who find that many of the dyes do in fact possess very powerful desensitising properties * (for details, see p. 676). These compounds, moreover, have other properties which, although varying within wide limits, frequently enhance the practical value of the dyes as desensitisers. At the low concentration at which they are applied, only slight staining of the emulsion is produced, and this staining is completely bleached subsequently by the acid fixing bath. The desensitising action of many of the dyes is not adversely affected by contact with neutral or alkaline developer solutions, and is in some cases actually enhanced. Furthermore, the application of certain of these compounds as desensitisers does not seriously impair the latent image in the exposed emulsion, nor does it cause undue fogging during the subsequent development. It is obvious that by varying the substituents in the 3-nitrosoindoles and also the heterocyclic methylene compounds with which they are condensed, a very large number of these new cyanine dyes can be prepared, and a wide choice of compound is thus available for photographic application.

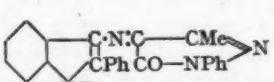
Other types of compounds containing reactive methylene groups fall into two classes, according to their reaction with our nitrosoindoles. The members of the first class undergo normal condensation with loss of water; since no question of quaternary salt formation is involved, the mechanism of this reaction is almost certainly not identical with that previously described. Thus ethyl cyanoacetate condensed with 3-nitroso-2-phenyl-1-ethylindole (I), giving 3-*carbethoxycyanomethyleneamino*-2-*phenyl*-1-*ethylindole* (XV); dibenzoylmethane gave 3-*dibenzoylmethyleneamino*-2-*phenyl*-1-*ethylindole* (XVI); 1-phenyl-3-methylpyrazolone gave 3-1′-*phenyl*-3′-*methyl*-4′-*pyrazolylamino*-2-*phenyl*-1-*ethylindole* (XVII).



(XV.)



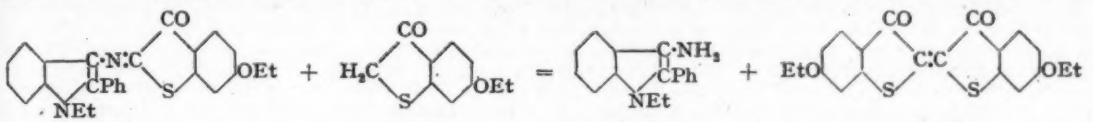
(XVI.)



(XVII.)

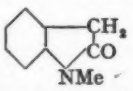
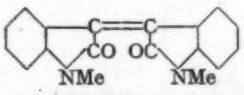
* Patent protection pending.

In the second class, however, 6-ethoxythioindoxyl * (XVIII) gave 6 : 6′-diethoxythioindigotin (XIX), and 6 : 7-benzthioindoxyl * similarly gave 6 : 7 : 6′ : 7′-dibenzthioindigotin; furthermore, 1-methyloxindole (XX) gave 1 : 1′-dimethyl*iso*indigotin (XXI). The members of this second class therefore undergo oxidation



(XXII.) (XVIII.) (XXIII.) (XIX.)

by the nitrosoindole. It is almost certain, however, that the initial reaction of members of this class is identical with that of the first class above; *e.g.*, that 6-ethoxythioindoxyl (XVIII) undergoes simple condensation to the aza-derivative (XXII). The latter, however, has the normal properties of an anil, and readily

(XX.)   (XXI.)

reacts with another molecule of the original methylene compound (XVIII) to give the 6 : 6′-diethoxythioindigotin (XIX). This mechanism must in each such case involve the formation of 3-*amino*-2-*phenyl*-1-*ethylindole* (XXIII). The nature of this amine renders its isolation from the above reaction mixtures very difficult; we have prepared it, however, by direct reduction of the nitrosoindole (I). Confirmation of the mechanism of this reaction is given by the work of Stollé *et al.* (*J. pr. Chem.*, 1930, **128**, 1), who showed that 1-methyloxindole (XX) also gave 1 : 1′-dimethyl*iso*indigotin (XXI) when boiled with *p*-nitrosodimethylaniline; clearly in this reaction the anil must have been the essential intermediate product.

Experimental.

The preparation of the indoles and their nitroso-derivatives is described first, and then the condensation derivatives of each nitrosoindole in turn. Solvents used for recrystallisation are given in parenthesis after the name of the compound concerned.

2-Phenyl-1-ethylindole and its 3-nitroso-derivative (I) were prepared as described by Crowther, Mann, and Purdie (*loc. cit.*) : the latter compound was further characterised as its *picrate*, reddish-orange needles (alcohol), m. p. 141—143° (Found : C, 55·4; H, 4·0. $C_{16}H_{14}ON_2,C_6H_3O_7N_3$ requires C, 55·1; H, 3·6%).

Reduction.—Zinc dust (8 g.) and concentrated hydrochloric acid (27 c.c.) were added in alternate small portions during 1 hour to a solution of the above nitrosoindole (5 g.) in boiling alcohol (100 c.c.). The deep green solution became red, and later pale yellow. The solution was then boiled for a further 30 minutes, cooled, and slowly diluted with water (200 c.c.). The pale brown precipitate, recrystallised from very dilute hydrochloric acid (charcoal), gave the *monohydrated hydrochloride* of 3-*amino*-2-*phenyl*-1-*ethylindole* (XXIII), m. p. 238—239° (Found : C, 66·6; H, 6·9; N, 9·8; Cl, 12·0. $C_{16}H_{16}N_2,HCl,H_2O$ requires C, 66·1; H, 6·5; N, 9·6; Cl, 12·2%) : 3·0 g., 52%. This salt crystallised from alcohol as the *mono-ethyl-alcoholate*, m. p. 238—239° (Found : C, 67·5; H, 7·1. $C_{16}H_{16}N_2,HCl,C_2H_6O$ requires C, 67·8; H, 7·2%).

5-*Ethoxy*-2-*phenyl*-1-*ethylindole.*—(*a*) A mixture of *p*-phenetidine (396 g.) and ethyl bromide (342 g.; 1·1 mols.), when set aside in a securely stoppered thick-walled bottle for 12 hours, became almost solid. The bottle was then heated at 60° for 4 hours. An aqueous solution of the product was basified and extracted with ether (500 c.c.). The solvent was removed from the dried extract, and the residue on distillation gave two fractions, (i) b. p. 129—132°/15 mm. (108 g.); (ii) b. p. 132—135°/15 mm. (305 g., 65%) : fraction (ii) was pure *N*-*ethyl*-p-*phenetidine* (Found : C, 72·7; H, 9·25. $C_{10}H_{15}ON$ requires C, 72·7; H, 9·1%), but fraction (i) was not quite pure.

(*b*) A solution of sodium nitrite (130 g.) in water (460 c.c.) was added during 20 minutes to a mixture of fraction (ii) above (305 g.; 1 mol.), concentrated hydrochloric acid (270 c.c.), and crushed ice (800 g.), the temperature being kept below 10°. After 2 hours' stirring, the dark brown, crystalline *N*-nitroso-*N*-ethyl-*p*-phenetidine (150 g., 42%) was collected; m. p. 23·5—24·5°. [Fraction (i) above, similarly treated, gave a second crop, 46 g.] . This nitrosoamine could not be distilled even in a vacuum, and further purification was not attempted.

(*c*) The reduction of the above nitrosoamine to *as.*-*p*-phenetylethylhydrazine, $EtO{\cdot}C_6H_4{\cdot}NEt{\cdot}NH_2$, was attempted under various conditions, but the product was always contaminated with *N*-ethylphenetidine; these compounds have b. p.'s lying close together and cannot be separated satisfactorily by distillation. The following method, however, gives a sample of the hydrazine pure enough for indole formation by a Fischer synthesis. A solution of the nitrosoamine (196 g.) in acetic acid (285 c.c.) was added during 4·5 hours to a well-stirred mixture of zinc dust (285 g.) and water (430 c.c.), the temperature being kept between 10° and 20° : below this range, reduction ceased, whereas above it considerable reduction of the hydrazine occurred. The final mixture was stirred for 2 hours, then warmed to 60°, and filtered : the residue was washed with 5% hydrochloric acid (500 c.c.). The united filtrate and washings were cooled, basified, and extracted with ether. After drying and removal of the solvent, distillation in coal-gas gave two fractions : (i) b. p. 101—106°/0·7 mm., 23 g., (ii) b. p. 107—113°/0·7 mm., 98 g. Fraction (ii) on redistillation gave two fractions, (iii) b. p. 109—111°/0·7 mm., 56·6 g. (Found : C, 73·8; H, 9·8; N, 11·0. $C_{10}H_{16}ON_2$ requires C, 66·7; H, 8·9; N, 15·6%); (iv) b. p. 111—113°/0·7 mm., 22·8 g. (Found : C, 69·0; H, 9·2; N, 13·9%). Fraction (iii) clearly contained a high proportion of the amine, and fraction (iv) of the hydrazine.

(*d*) Fraction (iv) (11·6 g.), acetophenone (7·9 g.; 1 mol.), and acetic acid (0·3 g.) were heated together at 100° for 5 minutes, and powdered zinc chloride (50 g.) then added. A vigorous reaction occurred, and the temperature rose to 170°; it was then maintained at 150° for 10 minutes. The cold product was extracted with dilute hydrochloric acid, and the insoluble residue taken up in benzene. The dried benzene extract was distilled in coal-gas, 5-*ethoxy*-2-*phenyl*-1-*ethylindole* being obtained as a viscous oil, b. p. 200—210°/0·7 mm. : 5·2 g., 30%. The oil readily solidified, and gave colourless crystals (acetic acid, alcohol), m. p. 112—113° (Found : C, 84·6; H, 7·2. $C_{18}H_{19}ON$ requires C, 81·5; H, 7·2%. Satisfactory carbon values could not be obtained).

* These substituted thioindoxyls were chosen because their $>CH_2$ groups were known to have high reactivity (Harley-Mason and Mann, J., 1942, 404).

3-*Nitroso*-5-*ethoxy*-2-*phenyl*-1-*ethylindole*.—A solution of sodium nitrite (1·68 g.; 1·7 mols.) in water (3 c.c.) was slowly added to one of the indole (3·7 g.) in acetic acid (100 c.c.). After 2 hours the mixture was diluted with water, and the precipitated 3-*nitroso*-derivative collected: green crystals (alcohol), m. p. 136—137·5° (Found: C, 73·3; H, 6·6; N, 9·5. $C_{18}H_{18}O_2N_2$ requires C, 73·5; H, 6·1; N, 9·5%); 1·2 g., 29%.

1 : 2-*Diphenylindole*.—Acetic acid (0·5 c.c.) was added to a mixture of *as*.-diphenylhydrazine (55 g.) and acetophenone (36 g.; 1 mol.): a cloudiness developed as hydrazine formation proceeded. Powdered dry zinc chloride (160 g.) was added; the mixture, when cautiously heated, first became almost solid, then a vigorous reaction occurred, the temperature rising spontaneously from 130° to 200°. After 5 minutes at this temperature, the mixture was cooled and extracted with dilute hydrochloric acid, and the residual indole taken up in ether (600 c.c.). After removal of the ether from the dried extract, the residue was fractionally distilled, 1 : 2-*diphenylindole* being obtained first as a syrup, b. p. 198—200°/0·7 mm. (20 g., 25%), which however readily solidified, and gave colourless crystals (acetic acid, alcohol), m. p. 80—82° (Found: C, 89·3; H, 5·8; N, 5·5. $C_{20}H_{15}N$ requires C, 89·2; H, 5·6; N, 5·2%). Pfulf (*Annalen*, 1887, **239**, 223) claimed to have prepared this indole as a viscous oil.

Sodium nitrite (2·5 g.; 1·6 mols.) in water (5 c.c.) was added to a solution of the indole (6 g.) in acetic acid (200 c.c.). After 1 hour, the green crystals of 3-*nitroso*-1 : 2-*diphenylindole* which had separated were collected (4·3 g.), a further crop (0·8 g., 77% in all) being obtained by diluting the filtrate with water: m. p. 200—202° (alcohol) (Found: C, 80·5; H, 4·4; N, 9·55. $C_{20}H_{14}ON_2$ requires C, 80·5; H, 4·7; N, 9·4%).

1 : 2-Dimethylindole was prepared by the following modification of Degen's method (*Annalen*, 1886, **236**, 152). Glacial acetic acid (0·3 c.c.) was added to a mixture of phenylmethylhydrazine (27 g.) and acetone (19·4 c.c.; 1 mol.): heat was immediately generated, and water separated as hydrazone formation proceeded. The mixture was set aside overnight and then refluxed on a water-bath for 3 hours. The product was dried (sodium sulphate) and distilled, the hydrazone being obtained as a pale yellow oil, b. p. 112—117°/20 mm.: 32·8 g. (92%). A mixture of the hydrazone (32·8 g.) and powdered anhydrous zinc chloride (160 g.) was then heated at 130° for 3 hours. The dark warm product was vigorously agitated with dilute sulphuric acid, and the residue then dissolved in benzene, dried (sodium sulphate), and distilled, 1 : 2-dimethylindole being obtained as a pale yellow oil, b. p. 145—149°/16 mm. (7·2 g., 24%); it readily solidified, giving colourless crystals (petrol), m. p. 52—54°. Degen (*loc. cit.*) gives m. p. 56°.

The *dinitroso*-derivative (II) was best prepared as follows. A solution of 1 : 2-dimethylindole (1 g.) in acetic acid (60 c.c.) was cooled until the acid began to crystallise. Finely powdered sodium nitrite (0·5 g.; 1 mol.) was slowly added with stirring, the mixture becoming dark green and then greenish-brown, and a green solid separating. The mixture was set aside until it reached room temperature, and then filtered. The green 3-*nitroso*-1-*methyl*-2-*oximinomethylindole* (II) thus collected (0·4 g., 27%) was washed with water, dried, and recrystallised from alcohol: m. p. 173° (decomp., effer.) (Found: C, 59·4; H, 4·7; N, 20·7. $C_{10}H_9O_2N_3$ requires C, 59·1; H, 4·4; N, 20·7%). The use of larger proportions of sodium nitrite in the above preparation caused the compound (II) to be contaminated with other products.

1-*Phenyl*-2-*methylindole*.—Acetic acid (0·3 c.c.) was added to a mixture of diphenylhydrazine (110 g.) and acetone (66 c.c.; 1·2 mols.), water rapidly separating. The mixture was refluxed for 6 hours, acetic acid (200 c.c.) and powdered zinc chloride (50 g.) then added, and the refluxing continued for another 8 hours. The dark solution was vigorously stirred with much dilute hydrochloric acid, and the residue dissolved in ether, dried (sodium sulphate), and distilled: the crude *indole* was obtained as a pale yellow oil. b. p. 132—170°/0·4 mm. (44 g., 35%), no definite fraction occurring within this range. The addition of a small quantity of alcohol to the distillate, however, caused the indole to solidify: colourless crystals (alcohol), m. p. 58—58·5° (Found: C, 86·6; H, 6·5; N, 6·3. $C_{15}H_{13}N$ requires C, 86·9; H, 6·3; N, 6·8%).

A solution of this indole (2·0 g.) in acetic acid (50 c.c.) was chilled until almost solid. It was vigorously stirred whilst a solution of sodium nitrite (1·48 g.; 2·2 mols.) in water (2 c.c.) was rapidly added: the acetic acid melted and a precipitate appeared. After 1 hour at room temperature, the greenish-brown solid was collected, and washed with water and then cold alcohol, the brown impurity being thus removed. The residual 3-*nitroso*-1-*phenyl*-2-*oximinomethylindole* (III) thus obtained (1·8 g., 70%) was recrystallised from alcohol and then benzene: pale green crystals, m. p. 186° (decomp.) (Found: C, 67·9; H, 4·5; N, 15·7. $C_{15}H_{12}O_2N_3$ requires C, 67·9; H, 4·15; N, 15·8%). The use of smaller proportions of sodium nitrite in the above preparation gave either a mixture of (III) with unchanged indole, or ill-defined brown amorphous products from which no definite compound could be isolated.

The derivatives (or other products) obtained from each of the above nitrosoindoles are given in turn below.

For the preparation of the cyanine dyes, sodium hydroxide could be used as a catalyst only for those condensations involving α- or γ-picoline methiodides: its use in other condensations gave impure products. Piperidine could be advantageously used, however, for all condensations requiring a catalyst. The colour of the crystalline cyanine dyes, being largely determined by surface reflexion, usually differed from that of their solutions in organic solvents. The colours of the solutions varied from dark reddish-brown to deep permanganate or reddish-violet: the colours of the crystalline dyes are specifically stated below.

Derivatives from 3-*Nitroso*-2-*phenyl*-1-*ethylindole* (I).—(1) (2-*Phenyl*-1-*ethyl*-3-*indole*)(1-*methyl*-2-*pyridine*)-α-*azadimethincyanine iodide* (IV). A solution of the nitrosoindole (2 g.), α-picoline methiodide (1·88 g.; 1 mol.), and piperidine (0·3 c.c.) in alcohol (50 c.c.) was refluxed for 5 hours, the colour becoming deep reddish-brown. The precipitated *cyanine iodide* (1·7 g., 46%) was collected from the cold solution; when washed and recrystallised from alcohol, it was obtained as reddish-brown crystals, m. p. 214—216° (Found: C, 59·1; H, 5·0; N, 9·2; I, 26·9. $C_{23}H_{22}N_3I$ requires C, 59·1; H, 4·7; N, 9·0; I, 27·2%). The piperidine could be replaced by 5% aqueous sodium hydroxide (0·3 c.c.).

(2) The corresponding (1-*methyl*-2-*quinoline*) *cyanine iodide* (V) was similarly prepared by using quinaldine methiodide (2·3 g.; 1 mol.). The permanganate-coloured solution was cooled, and the crude iodide collected (2·1 g., 51%); greenish-brown crystals (methyl alcohol), m. p. 218—219° (Found: C, 63·1; H, 4·8; N, 8·5; I, 24·6. $C_{27}H_{24}N_3I$ requires C, 62·7; H, 4·6; N, 8·1; I, 24·6%).

(3) Repetition of Experiment (1), quinaldine ethiodide (2·4 g.; 1 mol.) being used, gave a rapid reaction; the solution became permanganate-coloured immediately on boiling. After 7 hours' refluxing, cooling gave brownish-green crystals (1·5 g., 35%) of (2-*phenyl*-1-*ethyl*-3-*indole*) (1-*ethyl*-2-*quinoline*)-α-*azadimethincyanine iodide* (alcohol), m. p. 209—210° (Found: C, 63·6; H, 5·2; N, 7·75; I, 24·0. $C_{28}H_{26}N_3I$ requires C, 63·3; H, 4·9; N, 7·9; I, 23·9%). A small second crop was obtained by concentrating the mother-liquor.

(4) Experiment (1) was repeated, using however γ-picoline methiodide (1·88 g.) in methyl alcohol (30 c.c.) with 5% aqueous caustic soda (0·5 c.c.) as a catalyst and 12 hours' refluxing. The (1-*methyl*-4-*pyridine*) *cyanine iodide* (VI) (1·1 g., 30%) separated as reddish-brown crystals (methyl alcohol), m. p. 204—205° (Found: C, 59·3; H, 5·0; N, 9·25; I, 27·2. $C_{23}H_{22}N_3I$ requires C, 59·1; H, 4·7; N, 9·0; I, 27·2%).

γ-Picoline methiodide was readily prepared without a solvent: colourless crystals (acetone containing some methyl alcohol), m. p. 148—150° (Found: N, 6·0. Calc. for $C_7H_{10}NI$: N, 6·0%). Clemo and Gourlay (J., 1938, 478) give m. p. 149—150°.

(5) A solution of the nitrosoindole (2 g.), lepidine methiodide (2·3 g.; 1 mol.), and piperidine (0·1 c.c.) in alcohol

(50 c.c.) was refluxed for 3 hours, a violet coloration rapidly developing and solid dye separating. Filtration of the cold mixture furnished brownish-green crystals (2·8 g., 75%) of the (1-*methyl*-4-*quinoline*) *cyanine iodide* (VII) : recrystallisation from alcohol furnished the *mono-alcoholate*, m. p. 233—234° (Found : C, 61·9; H, 5·2; N, 7·6; I, 22·6. $C_{27}H_{24}N_2I,C_2H_6O$ requires C, 61·8; H, 5·4; N, 7·5; I, 22·5%). Long exposure in a vacuum over phosphoric oxide gave the solvent-free *iodide*, of unchanged m. p. (Found : C, 62·5; H, 4·6; N, 8·05; I, 24·7. $C_{27}H_{24}N_2I$ requires C, 62·7; H, 4·6; N, 8·1; I, 24·6%).

(6) The use of lepidine ethiodide (2·4 g. ; 1 mol.) in Expt. (5) gave brownish-green crystals (3·2 g., 75%) of the (1-*ethyl*-4-*quinoline*)*cyanine iodide* (as VII), iridescent green crystals from alcohol, m. p. 230—231° (Found : C, 63·1; H, 5·1; N, 7·8; I, 24·0. $C_{28}H_{26}N_2I$ requires C, 63·3; H, 4·9; N, 7·9; I, 23·9%).

(7) When a solution of the nitrosoindole (1 g.), 1 : 3 : 3-trimethyl-2-methyleneindoline (IX) (0·71 g. ; 1 mol.), and piperidine (0·1 c.c.) in alcohol (50 c.c.) was boiled for 7 hours, the colour of the solution darkened, but on cooling, the unchanged nitrosoindole crystallised. When, however, 2 : 3 : 3-trimethylindolenine methiodide (1·2 g. ; 1 mol.) was used, the solution rapidly developed a deep red colour on boiling without a catalyst. After 8 hours' refluxing, the solution was cooled : reddish-brown needles (1 g., 47%) of the (1 : 3 : 3-*trimethyl*-2-*indolenine*) *cyanine iodide* (VIII) separated : m. p. 220—221° after recrystallisation from alcohol (Found : C, 62·6; H, 5·3; N, 8·0; I, 23·8. $C_{29}H_{28}N_2I$ requires C, 63·0; H, 5·25; N, 7·9; I, 23·8%).

Piggott (U.S.P. 2,016,836) has described the nitration of 2 : 3 : 3-trimethylindolenine metho-hydrogen sulphate, whereby two isomeric mononitro-1 : 3 : 3-trimethyl-2-methyleneindolines, m. p. 100° and 140—143°, were obtained; the former gave a mononitro-2 : 3 : 3-trimethylindolenine methobromide, m. p. 256°. The position of the nitro-groups in these compounds was not determined. To ascertain whether cyanine formation was affected by substituents, the above methobromide (1·2 g.) was refluxed in alcohol (40 c.c.) with the nitrosoindole (1 g. ; 1 mol.) for 6 hours. The deep red solution was cooled and poured into ether (400 c.c.). The precipitated reddish-brown crystals (0·7 g., 33%) of the (*nitro*-1 : 3 : 3-*trimethyl*-2-*indolenine*) *cyanine bromide*, recrystallised from amyl alcohol, separated as a *monohydrate*, m. p. 224—225° (Found : C, 60·7; H, 5·2; N, 10·2; Br, 15·0. $C_{28}H_{27}O_2N_4Br,H_2O$ requires C, 61·2; H, 5·3; N, 10·2; Br, 14·6%).

(8) When a mixture of the nitrosoindole (2 g.) and 2-methylbenzthiazole ethiodide (2·44 g. ; 1 mol.) in alcohol (40 c.c.) was boiled, reaction readily occurred without a catalyst, the solution becoming permanganate-coloured. After 2 hours' refluxing and subsequent cooling, the iridescent red crystals (3·4 g., 79%) of the (1-*ethyl*-2-*benzthiazole*) *cyanine iodide* (X) were collected : after crystallisation from alcohol, m. p. 212—213° (Found : C, 58·3; H, 4·9; N, 7·7; I, 23·3. $C_{26}H_{24}N_2IS$ requires C, 58·1; H, 4·5; N, 7·8; I, 23·6%).

(9) Smith and Sapiro (*Trans. Roy. Soc. S. Africa*, 1929, **18**, 229) describe 2-methyltetrahydrobenzthiazole methiodide as an extremely deliquescent solid, exceedingly soluble in water and alcohol : they give an analysis but no m. p. We find that the methiodide, recrystallised from absolute alcohol, has m. p. 114—116° with slight preliminary softening, if great care is taken to ensure that the specimen is dry. The use of this methiodide (2·4 g.) in the previous experiment, with piperidine as a catalyst, gave scarlet crystals (2·0 g., 47%) of the (1-*methyl*-2-*tetrahydrobenzthiazole*) *cyanine iodide* (XI), m. p. 224° after recrystallisation from alcohol (Found : C, 57·1; H, 5·1; N, 7·6; I, 25·3. $C_{25}H_{26}N_2IS$ requires C, 56·9 H, 4·9; N, 8·0; I, 24·1%). Consistent values for iodine could not be obtained.

(10) Repetition of Expt. (8), 2-methylbenzselenazole methiodide (2·7 g. ; 1 mol.) in alcohol (60 c.c.) being used, rapidly gave a deep-red solution from which crystals separated after 30 minutes' boiling. After 5 hours' refluxing, the solution was cooled, and the greenish-brown iridescent needles (2·2 g., 48%) of the (1-*methyl*-2-*benzselenazole*) *cyanine iodide* (as X) collected, washed with water, methyl alcohol and ether, and recrystallised from methyl alcohol : m. p. 223° (decomp.) (Found : C, 50·7; H, 3·7; N, 7·4; I, 22·4. $C_{25}H_{23}N_2ISe$ requires C, 52·6; H, 3·9; N, 7·4; I, 22·3%. Low and inconsistent carbon values were always obtained).

(11) A mixture of the nitrosoindole (2·65 g.), ethyl cyanoacetate (1·20 g. ; 1 mol.), and zinc chloride (0·1 g.) was heated in a dry atmosphere at 135—140° for 3 hours. The viscous dark-red cold product solidified when mixed with alcohol : recrystallisation from alcohol gave orange crystals (1·5 g., 41%) of 3-*carbethoxycyanomethyleneamino*-2-*phenyl*-1-*ethylindole* (XV), m. p. 143—144° (Found : C, 72·9; H, 5·4; N, 12·2. $C_{21}H_{19}O_2N_3$ requires C, 73·0; H, 5·5; N, 12·2%).

(12) A mixture of the nitrosoindole (1 g.), dibenzoylmethane (0·9 g. ; 1 mol.), and zinc chloride (0·1 g.) was heated in coal-gas at 140° for 30 minutes. The cold red solid residue, crushed, washed with water, and recrystallised from alcohol, gave brown needles (0·7 g., 38%) of 3-*dibenzoylmethyleneamino*-2-*phenyl*-1-*ethylindole* (XVI), m. p. 161—163° (Found : C, 81·4; H, 5·45; N, 6·2. $C_{31}H_{24}O_2N_2$ requires C, 81·6; H, 5·3; N, 6·1%).

A similar condensation was attempted with acetylacetone, but no satisfactory product could be isolated.

(13) Expt. (12) was repeated, 1-phenyl-3-methylpyrazolone (0·70 g. ; 1 mol.) being used, with heating at 135—140° for 2 hours. The cold solid product, similarly treated, gave brown iridescent crystals (0·4 g., 25%) of 3-1′-*phenyl*-3′-*methyl*-4′-*pyrazolylamino*-2-*phenyl*-1-*ethylindole* (XVII), m. p. 207—208° (Found : C, 76·8; H, 5·7; N, 14·3. $C_{26}H_{22}ON_4$ requires C, 76·8; H, 5·4; N, 13·8%).

(14) A mixture of the nitrosoindole (1 g.), 6-ethoxythioindoxyl (XVIII) (0·79 g. ; 1 mol.), zinc chloride (0·1 g.), and acetic acid (10 c.c.) was refluxed at 130—135° for 30 minutes and then cooled, in a coal-gas atmosphere throughout. The red residue was triturated with alcohol and collected : one half, recrystallised from nitrobenzene, gave red crystals of 6 : 6′-diethoxythioindigotin (XIX), m. p. above 260° (Found : C, 62·3; H, 4·35. Calc. for $C_{20}H_{16}O_4S_2$: C, 62·5; H, 4·2%) ; the second half, subjected to reductive acetylation by the method of Harley-Mason and Mann (*loc. cit.*), gave diacetyldihydro-6 : 6′-diethoxythioindigotin (acetic acid), m. p. 224—225°, alone and when mixed with an authentic specimen.

(15) Repetition of Expt. (14), 6 : 7-benzthioindoxyl (0·80 g. ; 1 mol.) being used, and heating at 125° for 10 minutes, gave ultimately red crystals of 6 : 7 : 6′ : 7′-dibenzthioindigotin (nitrobenzene), m. p. above 290° (Found : C, 72·6; H, 3·4. Calc. for $C_{24}H_{12}O_2S_4$: C, 72·7; H, 3·0%).

(16) A mixture of the nitrosoindole (2 g.), 1-methyloxindole (XX) (1·2 g. ; 1 mol.), and zinc chloride (0·1 g.) was heated in coal-gas. It melted at 110°, and a vigorous reaction occurred at 140°, a red solid forming : the temperature was then kept at 135—140° for 2 hours. The cold product, crushed, washed with water and recrystallised from acetone, gave crimson needles (0·3 g., 25%) of 1 : 1′-dimethyl*iso*indigotin (XXI), m. p. 263—264° (Found : C, 74·0; H, 5·0; N, 9·6. Calc. for $C_{18}H_{14}O_2N_2$: C, 74·5; H, 4·8; N, 9·6%). Stollé (*loc. cit.*) gives m. p. 265°.

The nitrosoindole could not be condensed with rhodanine, in spite of a variety of conditions employed.

Derivatives from 3-*Nitroso*-2-p-*chlorophenyl*-1-*ethylindole*.—For the preparation of this nitrosoindole, see Crowther, Mann, and Purdie (*loc. cit.*).

(1) The nitrosoindole (2 g.), α-picoline methiodide (1·65 g. ; 1 mol.), and 5% aqueous sodium hydroxide (0·5 c.c.) in methyl alcohol (30 c.c.) were refluxed for 12 hours : hydriodic acid of constant b. p. (0·2 c.c.) was then added, and the mixture cooled. Brown needles (0·8 g., 18%) of (2-p-*chlorophenyl*-1-*ethyl*-3-*indole*)(1-*methyl*-2-*pyridine*)-α-*azadimethincyanine iodide* (as IV) separated ; m. p. 212—214°, after recrystallisation from methyl alcohol (Found : C, 54·7; H, 4·2; N, 8·8; Cl + I, 32·6. $C_{23}H_{21}N_3ClI$ requires C, 55·0; H, 4·2; N, 8·4; Cl + I, 32·4%).

(2) Repetition of Expt. (1), γ-picoline methiodide (1·65 g.) being used and 6 hours' refluxing, furnished reddish-

brown crystals (becoming green when crushed) (0·8 g., 18%) of the (1-*methyl*-4-*pyridine*) *cyanine iodide* (as VI) (methyl alcohol), m. p. 253—254° (Found: C, 54·9; H, 4·3; N, 8·1; Cl + I, 32·5%).

(3) Refluxing the nitrosoindole (1 g.), lepidine methiodide (1 g.; 1 mol.), and piperidine (0·3 c.c.) in methyl alcohol (40 c.c.) for 4 hours gave brown crystals having a green reflexion (1·6 g., 78%) of the (1-*methyl*-4-*quinoline*) *cyanine iodide* (as VII), which crystallised from methyl alcohol as a *mono-alcoholate*, m. p. 245—247° (Found: C, 57·7; H, 4·7; N, 7·1; Cl + I, 27·5. $C_{27}H_{23}N_3ClI,CH_4O$ requires C, 57·6; H, 4·6; N, 7·2; Cl + I, 27·8%).

(4) Repetition of Expt. (3), 2-methylbenzthiazole ethiodide (1·07 g.; 1 mol.) in ethyl alcohol (40 c.c.) being used, gave iridescent brownish-green crystals (1·3 g., 65%) of the (1-*ethyl*-2-*benzthiazole*) *cyanine iodide* (as X) (alcohol), m. p. 240—241° (Found: C, 55·0; H, 4·4; N, 7·3; Cl + I, 27·5. $C_{26}H_{23}N_3ClIS$ requires C, 54·6; H, 4·0; N, 7·35; Cl + I, 28·4%).

Derivative from 3-*Nitroso*-5-*ethoxy*-2-*phenyl*-1-*ethylindole*.—(1) The nitrosoindole (1 g.), lepidine methiodide (0·97 g.; 1 mol.), and piperidine (0·2 c.c.) in methyl alcohol (20 c.c.), refluxed together for 4 hours, furnished greenish-violet crystals (1·55 g., 80%) of (5-*ethoxy*-2-*phenyl*-1-*ethyl*-3-*indole*) (1-*methyl*-4-*quinoline*)-α-*azadimethincyanine iodide* (as VII), which crystallised from much methyl alcohol with 0·5 mol. of solvent; m. p. 244—245° (Found: C, 61·2; H, 5·3; N, 7·5; I, 22·3. $C_{29}H_{28}ON_3I,\frac{1}{2}CH_4O$ requires C, 61·3; H, 5·2; N, 7·3; I, 22·0%). Long exposure in a vacuum over sulphuric acid gave the solvent-free *iodide*, m. p. unchanged (Found: C, 61·9; H, 5·2. $C_{29}H_{28}ON_3I$ requires C, 62·0; H, 5·0%).

Derivatives from 3-*Nitroso*-1 : 2-*diphenylindole*.—(1) The nitrosoindole (2 g.), α-picoline methiodide (1·58 g.; 1 mol.), 5% aqueous sodium hydroxide (0·5 c.c.), and methyl alcohol (40 c.c.) were refluxed together for 12 hours. Hydriodic acid of constant b. p. (0·2 c.c.) was added, and cooling gave brown crystals (0·95 g., 27%) of (1 : 2-*diphenyl*-3-*indole*)(1-*methyl*-2-*pyridine*)-α-*azadimethincyanine iodide* (as IV), which crystallised from methyl alcohol as a *monohydrate*, which melted at *ca.* 125°, resolidified, and melted at 215—216° (Found: C, 60·3; H, 4·4; N, 7·8; I, 24·1. $C_{27}H_{22}N_3I,H_2O$ requires C, 60·8; H, 4·5; N, 7·9; I, 23·8%).

(2) Repetition of Expt. (1), γ-picoline methiodide (1·58 g.) being used, furnished reddish-brown crystals having an iridescent green surface reflexion (0·8 g., 23%) of the (1-*methyl*-4-*pyridine*) *cyanine iodide* (as VI), m. p. 276° (Found: C, 63·0; H, 4·9; N, 8·3; I, 25·3. $C_{27}H_{22}N_3I$ requires C, 62·9; H, 4·3; N, 8·15; I, 24·7%).

(3) The nitrosoindole (1 g.), lepidine methiodide (0·95 g.; 1 mol.), and piperidine (0·3 c.c.) in methyl alcohol (30 c.c.) were refluxed for 4 hours and then cooled. Reddish-brown crystals (1·8 g., 86%) of the (1-*methyl*-4-*quinoline*) *cyanine iodide* (as VII) separated: recrystallisation from methyl alcohol furnished a *mono-methyl alcoholate*, m. p. 180—183° with preliminary softening (Found: C, 63·9; H, 4·7; N, 6·8; I, 21·3. $C_{31}H_{24}N_3I,CH_4O$ requires C, 64·3; H, 4·7; N, 7·0; I, 21·3%).

(4) Refluxing a solution of the nitrosoindole (1 g.) and 2 : 3 : 3-trimethylindolenine methiodide (1 g.; 1 mol.) in alcohol (30 c.c.) gave ready condensation without a catalyst. After 4 hours' boiling, cooling gave crimson crystals (0·85 g., 44%) of the (1 : 3 : 3-*trimethyl*-2-*indolenine*) *cyanine iodide* (as VIII) (ethyl alcohol), m. p. 232—233° (Found: C, 65·8; H, 5·2; N, 7·2; I, 21·6. $C_{32}H_{28}N_3I$ requires C, 66·1; H, 4·8; N, 7·2; I, 21·9%).

(5) Repetition of Experiment (4), 2-methylbenzthiazole ethiodide (1·02 g.; 1 mol.) being used, gave crimson crystals (1·3 g., 66%) of the (1-*ethyl*-2-*benzthiazole*) *cyanine iodide* (as X), m. p. 204—205° after crystallisation from alcohol, in which it was only slightly soluble (Found: C, 61·2; H, 4·8; N, 7·1; I, 21·5. $C_{30}H_{24}N_3IS$ requires C, 61·5; H, 4·1; N, 7·2; I. 21·7%).

Derivatives from 3-*Nitroso*-1-*methyl*-2-*oximinomethylindole* (II).—A solution of the dinitrosoindole (II) (1 g.) and 2-methylbenzthiazole ethiodide (1·4 g.; 1 mol.) in alcohol (60 c.c.), when refluxed for 5 hours, rapidly developed a deep red colour and deposited reddish-brown crystals of (1-*methyl*-2-*oximinomethyl*-3-*indole*)(1-*ethyl*-2-*benzthiazole*)-α-*azadimethincyanine iodide*. The latter (0·9 g., 40%) were collected from the cold product, and recrystallised from alcohol; m. p. 209° (decomp.) (Found: C, 49·5; H, 4·2; N, 11·1; I, 26·5. $C_{30}H_{19}ON_4IS$ requires C, 49·0; H, 3·9; N, 11·4; I, 25·9%). The assumption that it is the 3-nitroso-group which has undergone condensation in the above reaction is based on analogy with the previous condensations.

We are indebted to the staff of Imperial Chemical Industries Ltd. (Dyestuffs Division) for the following report on the desensitising properties of the cyanine dyes:.

"The results tabulated below refer to the determination of the comparative useful desensitising effect of the dyes compared with that of Pinakryptol Yellow. The figures represent an accurate comparison between the dyes only when employed under the particular conditions defined. Alteration in these conditions (*e.g.*, concentration), the use of a different test emulsion, or alteration in the properties of the dye (*e.g.*, change of an anion leading to a change in solubility) would lead to different and largely unpredictable results.

"The method of evaluation is based on a conventional method of employing desensitisers in processing optically sensitised emulsions. The value of the dye solution for this purpose compared with a similar solution of Pinakryptol

Compound.	A.	B.	C.	Remarks.
Pinakryptol yellow	0 : 200	0	100	U.D.
3-*Nitroso*-2-*phenyl*-1-*ethylindole condensed with :*				
α-Picoline methiodide	40 : 160	0·19	9	U.D. Stain, nil.
Quinaldine methiodide	30 : 170	0·80	2060	N-U.D. Stain, nil.
Quinaldine ethiodide	30 : 170	0·47	1750	Stain, trace.
γ-Picoline methiodide	20 : 180	0·10	13	U.D. Stain, nil.
Lepidine methiodide	40 : 160	0·16	374	Slightly Unv.D. Stain, trace.
Lepidine ethiodide	40 : 160	0·24	558	U.D. Stain, nil.
2 : 3 : 3-Trimethylindolenine methiodide	30 : 170	0·02	79	U.D. Stain, trace.
Nitro-2 : 3 : 3-trimethylindolenine methobromide	100 : 100	0·11	26	U.D. Stain, nil.
2-Methylbenzthiazole ethiodide	100 : 100	0·40	664	U.D. Stain, nil.
3-*Nitroso*-2-p-*chlorophenyl*-1-*ethylindole condensed with :*				
α-Picoline methiodide	30 : 170	0·10	12	U.D. Stain, nil.
γ-Picoline methiodide	60 : 140	0·00	112	U.D. Stain, nil.
Lepidine methiodide	60 : 140	0·44	835	Stain, trace.
2-Methylbenzthiazole ethiodide	30 : 170	0·22	380	Slightly N-U.D. Stain, slight.
3-*Nitroso*-1 : 2-*diphenylindole condensed with :*				
α-Picoline methiodide	30 : 170	0·04	21	U.D. Stain, nil.
γ-Picoline methiodide	30 : 170	0·30	58	U.D. Stain, nil.
Lepidine methiodide	100 : 100	0·36	400	U.D. Stain, trace.
2 : 3 : 3-Trimethylindolenine methiodide	100 : 100	0·03	31	U.D. Stain, nil.
2-Methylbenzthiazole ethiodide	100 : 100	0·92	391	Unv.D. Stain, nil.

Yellow is deduced from a joint consideration of two factors, namely, the fog density, and the exposure required to give a density of 0·2 above the fog level. Values less than 0·2 for the former and greater than 25 for the latter (Pinakryptol Yellow having values of 0·0 and 100 respectively) approximately define the limiting properties of dye solutions of practical value. The dyes (VIII), the 2-*p*-chlorophenyl analogue of (VI), and perhaps (VII) are examples of desensitisers of probable practical value.

"*Method of evaluation.* The dye is dissolved in water containing a minimum proportion of ethyl alcohol to give a 0·02% solution stable at 20°. The photographic plate (Ilford S.R. Panchromatic) is bathed in the dye solution in total darkness with moderate agitation for 2 minutes. After removal of the surface liquid, the emulsion is exposed under a step wedge to a standard (tungsten) light source for a suitable time (predetermined by separate test exposures) such that an approximately negative reproduction of the wedge image is obtained on subsequent development in a fresh bath of the standard developer for 4 minutes. The plate is fixed (15 minutes), washed and dried.

"The standard developer and fixing bath have the following composition and were used at 21°±0·5°:

"*Developer.* Metol, 1·31 g., quinol, 3·83 g., anhydrous sodium carbonate, 15·4 g., anhydrous sodium sulphite, 22·2 g., potassium bromide, 0·55 g., water to make solution to 1 l.

"*Fixing bath.* Sodium thiosulphate, 340 g., potassium metabisulphite, 39 g., water to make solution to 1 l.

"From density measurements on the dry plates, the fog density and the relative exposures required to give a density of 0·2 above the fog level are determined in the usual way.

"In the Table opposite, Column A gives the alcohol–water ratio of the dye solution, Column B the relative overall fog density, and Column C the relative exposure to give density of 0·2 above fog. In the last column, the abbreviation 'U.D.' means uniform desensitisation, 'N.-U.D.' non-uniform desensitisation, and 'Unv.D.' uneven desensitisation."

We are greatly indebted to Imperial Chemical Industries, Ltd. (Dyestuffs Division), for facilities provided in support of this work.

THE UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August 30th*, 1944.]

NOTES.

Purification of Colchicine by Chromatography. By J. N. ASHLEY and J. O. HARRIS.

COLCHICINE is normally encountered as a yellow amorphous powder which cannot readily be prepared in a pure crystalline condition. It can be obtained in pale yellow needles by crystallisation from ethyl acetate of the amorphous residue left after removal of chloroform from the addition compound of colchicine with chloroform (Clewer, Green, and Tutin, J., 1915, **107**, 839), but the method is tedious and was unsatisfactory in our hands. It has now been found that pure crystalline colchicine can readily be obtained in good yield by the following procedure: A solution of colchicine (U.S.P.) (5 g.), m. p. 140—144°, in chloroform (50 c.c.) was passed through a column (15 cm. long, 1 cm. diameter) of alumina (B.D.H. chromatographic alumina) previously saturated with benzene, and the column afterwards washed down with chloroform (100 c.c.). After removal of the chloroform, the residual gum was triturated with a little anhydrous ether, an almost colourless residue (4·75 g.) of practically pure colchicine being obtained. This crystallised readily from ethyl acetate in very pale yellow needles, m. p. 155°, $[\alpha]_D^{17°}$ − 120·7° (Found: N, 3·6. Calc. for $C_{22}H_{25}O_6N$: N, 3·5%). Clewer *et al.* (*loc. cit.*) give $[\alpha]_D^{15·5°}$ − 120·3°. Crystallisation from benzene gave very pale yellow prisms, m. p. 140°, which contained 1 mol. of benzene of crystallisation (Found: C, 70·0; H, 6·4; N, 3·1. Calc. for $C_{22}H_{25}O_6N,C_6H_6$: C, 70·4; H, 6·5; N, 2·9%).

Elution of the column with methyl alcohol yielded a small amount of brown amorphous material, which could not be crystallised.

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β-Thymoxyethyldiethylamine. By CHARLES E. DALGLIESH.

THYMOXYETHYLDIETHYLAMINE (β-thymoxytriethylamine, Fourneau 929) is a substance of considerable pharmacological interest, but is not available in this country at the present time. It was first prepared by Einhorn and Rothlauf (*Annalen*, 1911, **382**, 256) by distillation of β-diethylaminoethyl thymyl carbonate in a vacuum, and was claimed to have b. p. 126°/18 mm. However, Einhorn (D.R.-P. 224,160) cited the b. p. as 157—159°/16 mm. Details of other methods of preparation or reliable values for the physical constants do not appear to be available, and I therefore record the following simple procedure.

β-Diethylaminoethanol (59 g.), treated with thionyl chloride (120 g.) by the method of Gough and King (J., 1928, 2426), gave β-chlorotriethylamine hydrochloride. Treatment of an ice-cold aqueous solution with dilute sodium hydroxide, followed by ether extraction and distillation, gave β-chlorotriethylamine (50 g., b. p. 66°/20 mm.). To a solution of thymol (50 g.) in alcohol (100 c.c.) was added a solution of sodium (7·5 g.) in alcohol (100 c.c.). After 15 minutes the solvent was removed by distillation, and the residue dissolved in chloroform (100 c.c.), β-chlorotriethylamine (47 g.) then being added with shaking. The temperature started to rise after 5 minutes, and the mixture was cooled in ice as soon as boiling commenced. The resultant, almost solid, product was diluted with alcohol (150 c.c.) and set aside for 1 hour; the liquid was then filtered, and the solid residue washed with ether. The combined ethereal filtrates were dried (sodium sulphate), subsequent distillation giving the required amine as an almost colourless liquid (72 g., 87% of the theoretical yield), b. p. 180°/18 mm., 114°/0·3 mm. (Found: C, 77·3; H, 10·8; N, 5·55. Calc. for $C_{16}H_{27}ON$: C, 77·1; H, 10·8; N, 5·6%).

The compound readily gives a *picrate*, crystallising from alcohol in yellow needles, m. p. 130—131° (Found: N, 11·8. $C_{16}H_{27}ON,C_6H_3O_7N_3$ requires N, 11·71%), and a *methiodide*, very soluble in alcohol, but precipitated by ether in white needles, m. p. 127—129° (Found: I, 32·1. $C_{17}H_{30}ONI$ requires I, 32·5%).

I would like to express my indebtedness to the Department of Scientific and Industrial Research for a grant.—THE UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, October 26th*, 1944.]

Preparation of 1-*Aminophthalaz-4-one.* By (Miss) E. F. M. Stephenson.

1-Chlorophthalaz-4-one (10 g.), ammonium carbonate (7 g.), and aqueous ammonia (*d* 0·940; 100 ml.) were heated in a stainless steel autoclave (oil-bath at 195—210°) for 21 hours and the product, after evaporation to dryness on the water-bath, was extracted repeatedly with boiling water. The first extractions contained the amine (4·3 g.), which was obtained in long colourless needles, m. p. 271—272° (corr.; decomp.), after several crystallisations from hot water (Found: C, 59·4; H, 4·5; N, 26·0. Calc. for $C_8H_7ON_3$: C, 59·6; H, 4·4; N, 26·1%). The later extractions contained mainly phthalaz-1 : 4-dione (1·8 g.). The amine was readily soluble in 10% sodium hydroxide solution and concentrated hydrochloric acid, very soluble in acetic acid, fairly soluble in alcohol and was converted by potassium nitrite and acetic acid at 0° into phthalaz-1 : 4-dione, identified by m. p. and mixed m. p. The dibenzoyl derivative (benzoyl chloride in pyridine for 5 hours), obtained as an oil after removal of the pyridine and crystallised by treatment with alcohol, had m. p. 252—253° (uncorr.; decomp.) after recrystallisation from trichloroethylene–alcohol (Found: N, 11·5. Calc. for $C_{22}H_{15}O_3N_3$: N, 11·4%).—The University, Melbourne. [*Received, August 29th*, 1944.]

Benzylamine-4-carboxylic Acid. By A. Albert and D. Magrath.

Current interest (*e.g.*, Mitchell, Rees, and Robinson, *Lancet*, 1944, i, 627) in the antibacterial action of homosulphanilamide (marfanil, benzylamine-4-sulphonamide) led to a request for benzylamine-4-carboxylic acid, which is structurally (but not necessarily biologically) related to homosulphanilamide in the same way as *p*-aminobenzoic acid is related to sulphanilamide.

The only recorded preparation of benzylamine-4-carboxylic acid is the lengthy synthesis by Günther (*Ber.*, 1890, **23**, 1060). It was more easily prepared by hydrogenating a mixture of 4-cyanobenzoic acid (23 g.), Raney nickel (about 5 g.), aqueous ammonia (60 ml.; *d* 0·88), and water (300 ml.) at atmospheric temperature and pressure. When the theoretical amount of hydrogen had been absorbed (6 hours), the violet solution was filtered, boiled until ammonia ceased to come off, clarified, and concentrated to small bulk. Yield, 80% (m. p. 342°). After recrystallisation from 18 parts of boiling water, cream-coloured crystals were obtained, m. p. 345° (decomp.) (sealed tube), soluble in about 70 parts of cold water and agreeing with Günther's description.

The 4-cyanobenzoic acid was prepared by a modification of the process of Valby and Lucas (*J. Amer. Chem. Soc.*, 1929, **51**, 2718), the yield being increased from 30% to 80%. Sodium nitrite (18·5 g.) and *p*-aminobenzoic acid (35 g.) were made into a paste with water and slowly stirred into a mixture of concentrated hydrochloric acid (75 ml.) and ice (100 g.). The excess of acid was then neutralised by the cautious addition of sodium hydroxide (7·7 g.) in water, with good cooling. The solution was slowly added to a preparation, made by heating and then cooling to 15°, of hydrated nickel sulphate (100 g.), potassium cyanide (73 g.), and water (600 ml.). After an hour, the mixture was warmed at 80° for ½ hour, cooled, and acidified with hydrochloric acid until no further precipitate formed. The precipitate was dried at 100° and refluxed for 4 hours with a mixture of benzene (1500 ml.) and ethanol (75 ml.) to decompose the co-ordination complex. The residue left after evaporation (m. p. 211°) was sublimed at 3 mm., giving pale cream crystals in 78—84% yield; m. p. 219°.—University of Sydney. [*Received, October 4th*, 1944.]

5-Nitro-4 : 6-diamino-2-methylpyrimidine and a Modified Procedure for the Preparation of Chloropyrimidines. By J. Baddiley and A. Topham.

In the course of investigations on purine synthesis in these laboratories, a sample of 5-nitro-4 : 6-diamino-2-methylpyrimidine was required. Huber and Hölscher (*Ber.*, 1938, **71**, 94) claim to have prepared this compound by the action of alcoholic ammonia on 4 : 6-dichloro-5-nitro-2-methylpyrimidine and report that it is readily soluble in benzene and alcohol and has m. p. 234°. On repeating the experiment described by these authors, we obtained a crystalline product which had no m. p. and was virtually insoluble in both benzene and alcohol. That this product is indeed *5-nitro-4 : 6-diamino-2-methylpyrimidine* follows from its ready reduction to the known 4 : 5 : 6-triamino-2-methylpyrimidine. The nature of the German workers' product is obscure, but its formation may possibly be bound up with the fact that the starting material for its preparation, 4 : 6-dichloro-5-nitro-2-methylpyrimidine, was described by them as having m. p. 37°, whereas the same substance prepared by us had m. p. 54—55°.

Attention is drawn to the preparation of 4 : 6-dichloro-5-nitro-2-methylpyrimidine from the corresponding dihydroxy-compound by heating with phosphoryl chloride and dimethylaniline. In the past, preparation of chloropyrimidines from hydroxypyrimidines has usually been effected by heating with phosphorus pentachloride, phosphoryl chloride or a mixture of these two substances, and in many cases it has proved very troublesome. Thus, for example, 2 : 4 : 6-trichloropyrimidine, a valuable intermediate for various purposes, has been obtained by heating barbituric acid with phosphoryl chloride in a continuously rotating sealed tube at 140° (Gabriel, *Ber.*, 1900, **33**, 3666); it may be readily prepared, however, by refluxing a mixture of barbituric acid, phosphoryl chloride, and dimethylaniline for only 5 minutes. This modified procedure, already reported from these laboratories for the preparation of 4 : 6-dichloropyrimidine (J., 1943, 574), has been used successfully for many pyrimidine derivatives and appears to be generally applicable. It is particularly useful in the case of pyrimidines containing nitro- or amino-groups, where the older methods are most frequently troublesome. As an additional example, the preparation of 4-chloro-6-amino-2-methylthiopyrimidine by the new method is also described.

4 : 6-Dichloro-5-nitro-2-methylpyrimidine.—Dimethylaniline (10 c.c.) was added carefully to a mixture of 5-nitro-4 : 6-dihydroxy-2-methylpyrimidine (8 g.) and phosphoryl chloride (40 c.c.), and the reaction completed by heating under reflux for 1 hour. The cooled solution was poured on ice, and the product extracted with ether. The extract, washed with sodium bicarbonate solution, dried over sodium sulphate, and evaporated, left an oil which distilled at 115°/20 mm., the distillate setting to a mass of pale yellow needles (3·7 g.), m. p. 54—55° (Found: C, 29·3; H, 1·6; N, 19·5. Calc. for $C_5H_3O_2N_3Cl_2$: C, 28·9; H, 1·4; N, 20·1%).

5-Nitro-4 : 6-diamino-2-methylpyrimidine.—Methanolic ammonia (25 c.c., saturated at 0°) was added slowly with shaking to an ice-cold solution of 4 : 6-dichloro-5-nitro-2-methylpyrimidine (2 g.) in methanol (25 c.c.). The mixture was allowed to warm to room temperature and after a further 10 mins. the solid which had separated was collected and washed with water. It was purified by dissolution in dilute hydrochloric acid and reprecipitation with ammonia. On heating, it decomposed without melting and it was virtually insoluble in benzene and alcohol (Found: C, 35·8; H, 4·1; N, 40·9. $C_5H_7O_2N_5$ requires C, 35·5; H, 4·1; N, 41·4%). Yield, 82%.

The above nitro-compound (1 g.) was suspended in alcohol (150 c.c.) and reduced with hydrogen at 100°/120 atms. during 3 hours, a Raney nickel catalyst being used. The catalyst was filtered off, and the clear solution evaporated to dryness. The residue sublimed at 100°/10^{-2} mm. in colourless prisms, m. p. 247°, undepressed by authentic 4 : 5 : 6-triamino-2-methylpyrimidine (m. p. 250°). Yield, 90%.

2 : 4 : 6-*Trichloropyrimidine.*—Barbituric acid (52 g.) was added portionwise during 5 minutes to a mixture of dimethylaniline (88·5 c.c.) and phosphoryl chloride (156 c.c.), and the whole refluxed for 5 minutes, cooled, and poured on ice (800 g.). The mixture was extracted with ether, the extract dried and evaporated, and the residual 2 : 4 : 6-trichloropyrimidine purified by distillation at 102°/18 mm. Yield, 46%.

4-*Chloro*-6-*amino*-2-*methylthiopyrimidine.*—6-Amino-4-hydroxy-2-methylthiopyrimidine (120 g.), phosphoryl chloride (450 c.c.), and dimethylaniline (200 c.c.) were refluxed together for 1 hour, the excess of phosphoryl chloride removed in a vacuum, and the residue poured on ice. Excess of aqueous ammonia was added, dimethylaniline removed by extraction with light petroleum (b. p. 60—80°), and the aqueous solution concentrated until solid began to separate. The chloro-compound, recrystallised from water, had m. p. 131°, undepressed by a specimen prepared according to Johnson and Johns (*Amer. Chem. J.*, 1905, **34**, 183). Yield, 65%.

The authors wish to thank Professor A. R. Todd, F.R.S., for his interest and advice.—THE UNIVERSITY, MANCHESTER. [*Received, September 25th*, 1944.]

The Conversion of Acridones into Acridines. By R. A. REED.

THE classical method of bringing about the above conversion by distillation with zinc dust, owing to the volatility of the acridones themselves, never gives good yields of acridine; much acridan is usually produced (cf. Kranzlein, *Ber.*, 1937, **70**, 1785). Clar's modification of the method (*Ber.*, 1939, **72**, 1645) gives no better result.

Better results are obtained by the method used by Kranzlein (*loc. cit.*) to prepare 2 : 3-dimethylacridine, in which the acridone is first reduced to the acridan, this after isolation being oxidised to the required acridine derivative. Ferric chloride appears to be the best oxidising agent for this purpose, although bromine, chromic acid and nitrous acid have all been used by other workers.

The acridone (0·5 g.) was heated with *iso*amyl alcohol (15 ml.) and treated with sodium (1 g.). The mixture was refluxed until the sodium had dissolved and all greenish fluorescence had vanished. The liquid was then steam-distilled to remove amyl alcohol, the cooled residue of acridan collected and dissolved in warm alcohol, and the cooled solution treated dropwise with aqueous ferric chloride until the green colour first given changed to yellow. Excess of ammonia was added to precipitate the ferrous hydroxide with the acridine. After the cold suspension had been filtered by gravity, the damp solid was extracted with boiling methyl alcohol, filtered hot, and the filtrate evaporated to crystallising point.

The following compounds were thus obtained from the corresponding acridones: 1-*methylacridan*, pale yellow needles, m. p. 82—83°, from aqueous methyl alcohol (Found: N, 7·2. $C_{14}H_{13}N$ requires N, 7·2%), and 1-methylacridine, pale yellow needles, m. p. 89° (Graebe and Locher, *Annalen*, 1894, **279**, 279, give m. p. 88°); 2-*methylacridan*, pale yellow leaflets, m. p. 152°, from aqueous alcohol (Found: N, 7·15%), and 2-methylacridine, pale yellow plates, m. p. 122—123°, from aqueous alcohol (Borsche, *Annalen*, 1910, **377**, 118, gives m. p. 125—126°); 3-methylacridan, yellow plates, m. p. 172°, from methyl alcohol (Found: N, 7·2%) (Kahn, *Annalen*, 1894, **279**, 274, gives m. p. 157°), and 3-methylacridine, m. p. 134° (Ullmann, *J. pr. Chem.*, 1889, **36**, 265, gives m. p. 134°); 4-*methylacridan*, pale yellow needles, m. p. 102—103°, from aqueous alcohol (Found: N, 7·2%), and 4-*methylacridine*, yellow needles, m. p. 98—99° (Found: N, 7·0. $C_{14}H_{11}N$ requires N, 7·25%).

Reduction of *N*-methylacridone produced *N*-methylacridan, pale yellow prisms, m. p. 95°, from methyl alcohol (Pictet and Patry, *Ber.*, 1902, **35**, 2536, give m. p. 96°).

5-Methylacridan was prepared by Sastry (J., 1916, **109**, 272) by reduction of 5-methylacridine with sodium amalgam in alcoholic solution and had m. p. 125—126°.

The position of the methyl group in the acridine nucleus makes little difference to the pH range over which the methylacridine changes colour when the solution is viewed under ultra-violet light. The change in all cases is green in acid to blue in alkaline solution and the pH ranges found for these compounds are: acridine 4·8—5·8, 1-methylacridine 4·8—5·8, 2-methylacridine 5·2—6·2, 3-methylacridine 5·0—6·0, 4-methylacridine 5·2—6·0.

All nitrogen microanalyses are by Dr. Weiler of Oxford.

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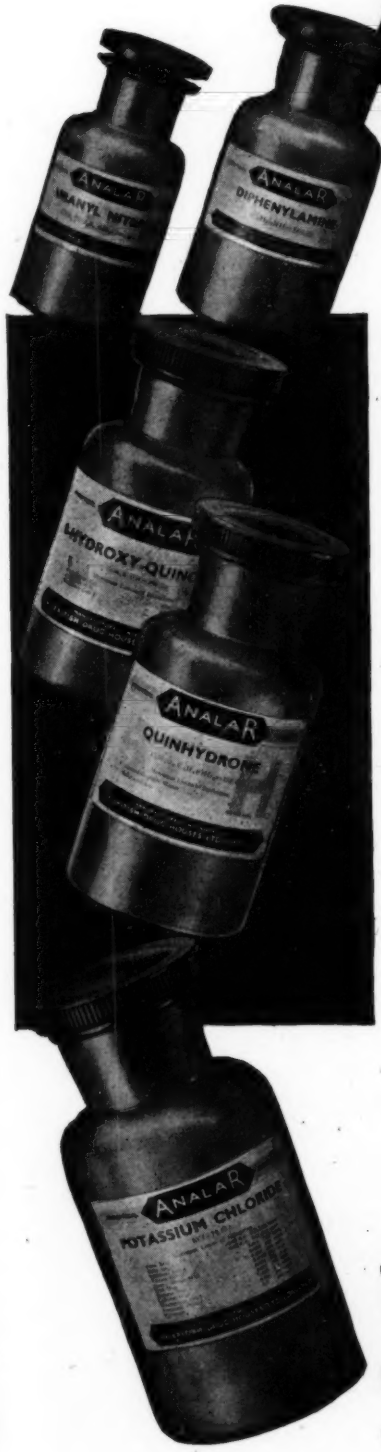

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